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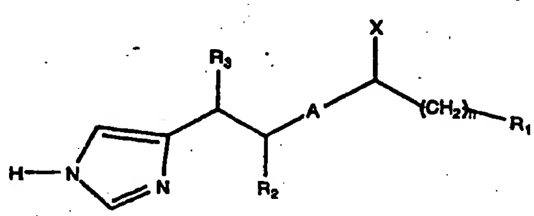

(1.0)

(57) Abstract

The present invention provides, in its principal aspect, compounds of general formula (1.0) or a pharmaceutically acceptable salt or hydrate thereof, wherein: where A is -NHCO-, $-N(CH_3)-CO-$, $-NHCH_2-$, $-N(CH_3)-CH_2-$, -CH=CH-, $-COCH_2-$, $-CH_2CH_2-$, $-CH(OH)CH_2-$, or -C≡C-; X is H, CH_3, NH_2, $NH(CH_3)$, $N(CH_3)_2$, OH, OCH_3, or SH; R_2 is hydrogen or a methyl or ethyl group; R_3 is hydrogen or a methyl or ethyl group; n is 0, 1, 2, 3, 4, 5, or 6; and R_1 is selected from the group consisting of (a) C_3 to C_8 cycloalkyl; (b) phenyl or substituted phenyl; (d) heterocyclic; (e) decahydronaphthalene and (f) octahydroindene; or R_1 and X may be taken together to denote a 5,6 or 6,6 saturated bicyclic ring structure when X is NH, O, or S. The individual stereoisomers of compounds of structural formula (1.0) above, as well as mixtures thereof, are also contemplated as falling within the scope of the present invention. The compounds of the present invention have H_3 histamine receptor antagonist activity. This invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier in combination with an effective amount of a compound of formula 1.0. The present invention also provides a method of treating conditions in which antagonism of histamine H_3 receptors may be of therapeutic importance.

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1H-4(5)-SUBSTITUTED IMIDAZOLE DERIVATIVES

TECHNICAL FIELD

This invention relates to compounds having pharmacological activity, to compositions containing these compounds, and to a medical method of treatment employing the compounds and compositions. More particularly, this invention concerns certain 1H-4(5)-substituted imidazole derivatives and their salts or solvates. These compounds have H_3 histamine receptor antagonist activity. This invention also relates to pharmaceutical compositions containing these compounds, and to a method of treating disorders in which histamine H_3 receptor blockade is beneficial.

BACKGROUND OF THE INVENTION

Histamine is a chemical messenger involved in various complex biological actions. When released, histamine interacts with specific macromolecular receptors on the cell surface or within a target cell to elicit changes in many different bodily functions. Various cell types including smooth muscle, blood cells, cells of the immune system, endocrine and exocrine cells as well as neurons respond to histamine by stimulating the formation of intracellular signals, including formation of phosphatidylinositol or adenylate cyclase. Evidence that histamine plays a role as a neurotransmitter was established by the mid to late 1970's (Schwartz, 1975) *Life Sci.* 17: 503-518. Immunohistochemical studies identified histaminergic cell bodies in the tuberomammillary nucleus of the posterior hypothalamus with widespread projections in the dicencephalon and telencephalon (Inagaki et al., 1988) *J. Comp. Neurol.* 273: 283-300.

Identification of two histamine receptors (H_1 and H_2) was reported to mediate the biochemical actions of histamine on neurons. Recently, studies have demonstrated the existence of a third subtype of histamine receptor, the histamine H_3 receptor (Schwartz et al., 1986) *TIPS* 8: 24-28. Various studies have now demonstrated that histamine H_3 receptors are found on the histaminergic nerve terminals in the brains of several species, including man (Arrang et al., 1983) *Nature* 302: 832-837. The H_3 receptor found on the histaminergic nerve terminal was defined as an autoreceptor and could intimately control the amount of histamine released from the neurons. Histamine, the natural compound, was

capable of stimulating this autoreceptor but when tested against known H_1 and H_2 receptor agonists and antagonists, a distinct pharmacological profile emerged. Furth r, H_3 receptors have been identified on cholinergic, serotoninergic and monoamine nerve terminals in the peripheral nervous system (PNS) and central nervous system including the cerebral cortex and cerebral vessels. These observations suggest that H_3 receptors are uniquely located to modulate histamine as well as other neurotransmitter release, and H_3 antagonists could be important mediators of neuronal activity.

As stated, CNS histaminergic cell bodies are found in the magnocellular nuclei of the hypothalamic mammillary region and these neurons project diffusely to large areas of the forebrain. The presence of histaminergic cell bodies in the tuberomamillary nucleus of the posterior hypothalamus, a brain area involved in the maintenance of wakefulness, and their projections to the cerebral cortex suggest a role in modulating the arousal state or sleep-wake. The histaminergic projection to many limbic structures such as the hippocampal formation and the amygdaloid complex suggest roles in functions such as autonomic regulation, control of emotions and motivated behaviors, and memory processes.

The concept that histamine is important for the state of arousal, as suggested by the location of histaminergic pathways, is supported by other types of evidence. Lesions of the posterior hypothalamus is well known to produce sleep. Neurochemical and electrophysiological studies have also indicated that the activity of histaminergic neurons is maximal during periods of wakefulness and is suppressed by barbiturates and other hypnotics. Intraventricular histamine induces the appearances of an arousal EEG pattern in rabbits and increased spontaneous locomotor activity, grooming and exploratory behavior in both saline and pentobarbital-treated rats.

In contrast, a highly selective inhibitor of histidine decarboxylase, the sole enzyme responsible for histamine synthesis, has been shown to impair waking in rats. These data support the hypothesis that histamine may function in modulating behavioral arousal. The role of the H_3 receptor in sleep-waking parameters has been recently demonstrated (Lin et al., 1990) *Brain Res.* <u>529</u>: 325-330. Oral administration of RAMHA, a H_3 agonist, caused a significant increase in deep slow wave sleep in the cat. Conversely, thioperamide, a H_3 antagonist, enhanced wakefulness in a dose-dependent fashion. Thioperamide has also been shown to increase wakefulness and decrease slow wave and REM sleep in rats. These findings are consistent with in vivo studies demonstrating that thioperamide caused an increase in

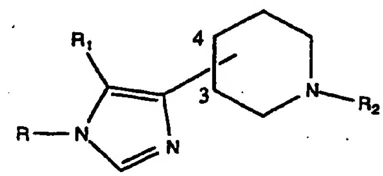
synth sis and release of histamine. Together, these data demonstrate that selective H_3 antagonists may be useful in the tr atment of arousal states and sleep disorders.

Serotonin, histamine, and acetylcholine have all been demonstrated to be diminished in the Alzheimer's (AD) brain. The histamine H_3 receptor has been demonstrated to regulate the release of each of these neurotransmitters. An H_3 receptor antagonist would therefore be expected to increase the release of these neurotransmitters in brain. Since histamine has been demonstrated to be important in arousal and vigilance, H_3 receptor antagonists might enhance arousal and vigilance via increasing levels of neurotransmitter release and improve cognition. Thus, the use of H_3 receptor antagonists in AD, attention deficit hyperactive disorders (ADHD), age-related memory dysfunction and other cognitive disorders would be supported.

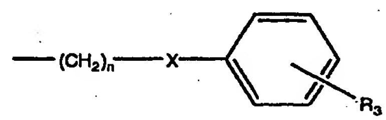
H_3 receptor antagonists may be useful in treating several other CNS disorders. It has been suggested that histamine may be involved in the control of sleep/wake states as well as states of arousal and alertness, cerebral circulation, energy metabolism, and hypothalmic hormone secretion. Recent evidence has indicated the possible use of H_3 antagonists in the treatment of epilepsy. Work has demonstrated an inverse correlation between the duration of clonic convulsions and brain histamine levels. Thioperamide, a H_3 antagonist, was also shown to significantly and dose-dependently decrease the durations of every convulsive phase after electrically-induced convulsions and increase the electroconvulsive threshold.

In spite of their low density, H_3 receptor binding sites can be detected outside the brain. Several studies have revealed the presence of H_3 heteroreceptors in the gastrointestinal tract, as well as upon neurons of the respiratory tract. Accordingly, an H_3 receptor antagonist may be useful in the treatment of diseases and conditions such as asthma, rhinitis, airway congestion, inflammation, hyper and hypo motility and acid secretion of the gastrointestinal tract. Peripheral or central blockade of H_3 receptors may also contribute to changes in blood pressure, heart rate and cardiovascular output and could be used in the treatment of cardiovascular diseases.

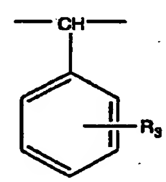
US 4,707,487 discloses c mpounds of the general formula:



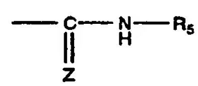
in which R_1 denotes H, CH_3, or C_2H_5 , R denotes H or R_2 and R_2 denotes an alkyl, piperonyl, 3-(1-benzimidazolonyl)-propyl group; a group of formula:



in which n is 0, 1, 2, or 3, X is a single bond or alternatively -O-, -S-, -NH-, -CO-, -CH=CH- or

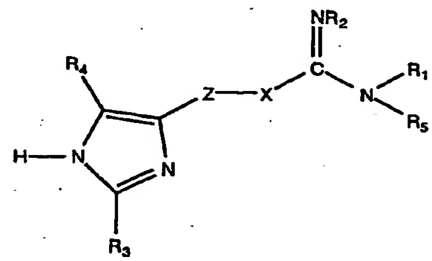


and R_3 is H, CH_3, F, CN or an acyl group; or alternatively a group of formula:

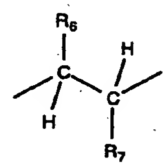


in which Z denotes an O or S atom or a divalent group NH, N-CH_3, or N-CN, and R_5 denotes an alkyl group, a cycloalkyl group which can bear a phenyl substituent, a phenyl group which can bear a CH_3 or F substituent, a phenylalkyl (C_1-C_3) group or a naphthyl, adamantyl, or p-toluenesulphonylgroup. It is also disclosed that these compounds antagonize the histamine H_3 receptors and increase the rate of renewal of cerebral histamine.

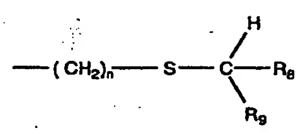
WO 92/15567 discloses compounds of general formula:



wherein: Z is a group of formula $(CH_2)_m$, wherein m = 1-5 or a group of the formula:

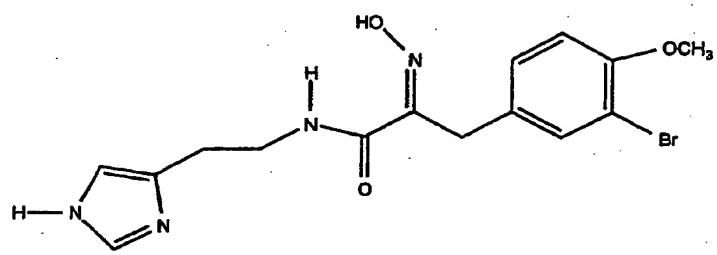


wherein R_6= $(C_1$-$C_3)$ alkyl, R_7 = $(C_1$-$C_3)$ alkyl; X represents S, NH, or CH_2; R_1 represents hydrogen, $(C_1$-$C_3)$ alkyl-, aryl $(C_1$-$C_{10})$ alkyl-, wherein aryl may optionally be substituted, aryl, $(C_5$-$C_7)$ cycloalkyl, $(C_1$-$C_{10})$ alkyl-, or a group of the formula:



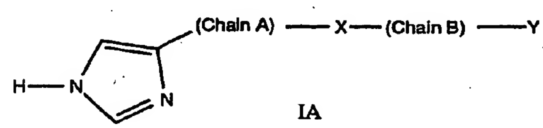
wherein n = 1-4, R_8 is aryl, aryl $(C_1$-$C_{10})$ alkyl-, $(C_5$-$C_7)$ cycloalkyl- or $(C_5$-$C_7)$ cycloalkyl $(C_1$-$C_{10})$ alkyl-, and R_9 is hydrogen, $(C_1$-$C_{10})$ alkyl- or aryl; R_2 and R_5 represent hydrogen, $(C_1$-$C_3)$ alkyl-, aryl or arylalkyl-, wherein aryl may optionally be substituted; R_3 represents hydrogen, $(C_1$-$C_3)$ alkyl, aryl, or arylalkyl-, wherein aryl may be substituted; and R_4 represents hydrogen, amino-, nitro-, cyano-, halogen-, $(C_1$-$C_3)$ alkyl, aryl, or arylalkyl-, wherein aryl may optionally be substituted; wherein aryl is phenyl, substituted phenyl, naphthyl, substituted naphthyl, pyridyl or substituted pyridyl. These compounds are reported to have agonistic or antagonistic activity on the histamine H_3 receptor.

US 5,217,986 discloses compound of formula:



This compound is reported to be active in an H_3 receptor assay, is reported to be an H_3 antagonist on guinea pig ileum, and accordingly is said to be useful in the treatment of diseases and conditions such as asthma, rhinitis, airway congestion, inflammation, cardiac arrhythmias, hypertension, hyper and hypo motility and acid secretion of the gastrointestinal tract, hypo- and hyper-activity of the central nervous system, migraine, and glaucoma.

WO 93/14070 discloses compounds of general formula:



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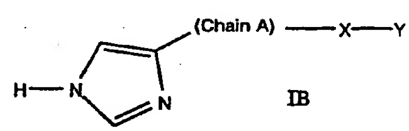
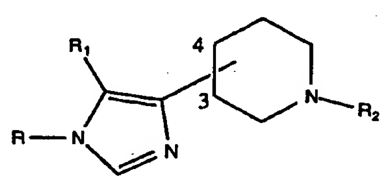


IB

Chain A represents a hydrocarbon chain, saturated or unsaturated, of 1-6 carbon atoms in length; X represents -O-, -S-, -NH-, -NHCO-, -N(alkyl)CO-, -NHCONH-, -NH-CS-NH-, -NHCS-, -O-CO-, -CO-O-, -OCONH-, -OCON(alkyl)-, -OCONH-CO-, -CONH-, -CON(alkyl)-, -SO-, -CO-, -CHOH-, -NR-C(=NR")-NR'-, R and R' can be hydrogen or alkyl and R" is hydrogen or cyano, or COY_1, Y_1 is alkoxy radical. Chain B represents an alkyl group $-(CH_2)_n-$, n = 0-5 or an alkyl chain of 2-8 carbon atoms interrupted by an oxygen

or sulfur atom or a group like -$(CH_2)_n$-O- or -$(CH_2)_n$-S- wherein n=1 or 2. Y represents $(C_1$-$C_8)$alkyl, $(C_3$-$C_6)$ cycloalkyl, bicycloalkyl, aryl, cycloalkenyl, heterocycle.

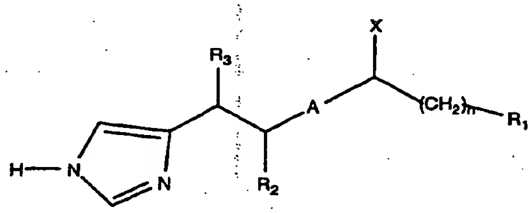
US 5,290,790 discloses compounds of the same general structure as US 4,707,487:



but specifically includes amides wherein R_2 is CO-NR'R" and R'R" are independently selected from the group consisting of (a) hydrogen; (b) phenyl or substituted phenyl; (c) alkyl; (d) cycloalkyl; and (e) alkylcycloalkyl. such as cyclohexylmethyl or cyclopentylethyl.

SUMMARY OF THE INVENTION

The present invention provides, in its principal aspect, compounds of the general formula:



(1.0)

where A is -NHCO-, -$N(CH_3)$-CO-, -$NHCH_2$-, -$N(CH_3)$-CH_2-, -CH=CH-, -$COCH_2$-, -CH_2CH_2-, -CH(OH)CH_2-, or —C≡C— ;

X is H, CH_3, NH_2, $NH(CH_3)$, $N(CH_3)_2$, OH, OCH_3, or SH;

R_2 is hydrogen or a methyl or ethyl group;

R_3 is hydrogen or a methyl or ethyl group;

n is 0, 1, 2, 3, 4, 5, or 6; and

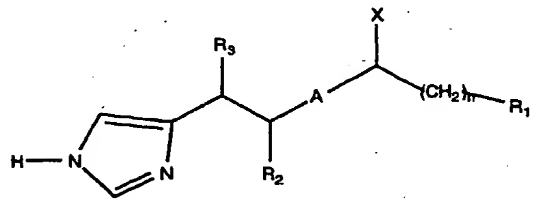
R_1 is selected from the group consisting of (a) C_3 to C_8 cycloalkyl; (b) phenyl or substituted phenyl; (d) heterocyclic; (e) decahydronaphthalene and (f) octahydroindene; or

R_1 and X may be taken together to denote a 5,6 or 6,6 saturated bicyclic ring structure when X is NH, O, S, or SO_2.

The pharmaceutically acceptable salts, hydrates and individual stereoisomers of compounds of structural formula (1.0) above, as well as mixtures thereof, are also contemplated as falling within the scope of the present invention.

This invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier in combination with an effective amount of a compound of formula (1.0). The present invention also provides a method of treating conditions in which antagonism of histamine H_3 receptors may be of therapeutic importance such as allergy, inflammation, cardiovascular disease (i.e. hyper or hypotension), gastrointestinal disorders (acid secretion, motility) and CNS disorders involving attention or cognitive disorders, (i.e., Alzheimer's, Attention Deficit Hyperactive Disorder, age-related memory dysfunction, stroke, etc), CNS psychiatric or motor disorders (i.e., depression, schizophrenia, obsessive-compulsive disorders, tourette's syndrome, etc.) and CNS sleep disorders (i.e., narcolepsy, sleep apnea, insomnia, disturbed biological and circadian rhythms, hyper and hyposomnolence, and related sleep disorders), epilepsy, hypothalamic dysfunction (i.e., eating disorders such as obesity, anorexia/bulimia, thermoregulation, hormone release) comprising administering an effective amount of a compound of formula (1.0) to a patient in need of such treatment.

DETAILED DESCRIPTION OF THE INVENTION



(1.0)

Preferably for compounds of formula (1.0),

A is -NHCO-, -N(CH_3)-CO-, -NHCH_2-, -N(CH_3)-CH_2-, -CH=CH-, -COCH_2-, -CH_2CH_2-, -CH(OH)CH_2-, or $-C\equiv C-$;

X is H, CH_3, NH_2, NH(CH_3), N(CH_3)$_2$, OH, OCH_3, or SH;

R_2 is hydrogen or a methyl or ethyl group;

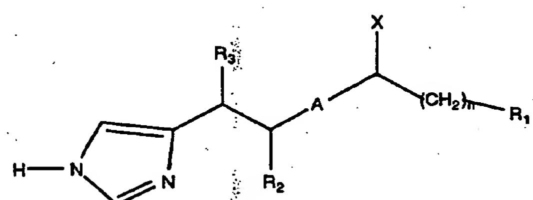
R_3 is hydrogen or a methyl or ethyl group;

n is 0, 1, 2, 3, 4, 5, or 6; and

R_1 is selected from the group consisting of (a) C_3 to C_8 cycloalkyl; (b) phenyl or substituted phenyl; (d) heterocyclic; (e) decahydronaphthalene and (f) octahydroindene; or

R_1 and X may be taken together to denote a 5,6 or 6,6 saturated bicyclic ring structure when X can be NH, O, or S.

More preferably, the present invention provides compounds of the general formula:



(1.0)

where A is -NHCH_2-, -N(CH_3)-CH_2-, -CH=CH-, -COCH_2-, -CH_2CH_2-, -CH(OH)CH_2-, or $-C\equiv C-$;

X is H, CH_3, NH_2, NH(CH_3), N(CH_3)$_2$, OH, OCH_3, or SH;

R_2 is hydrogen or a methyl or ethyl group;

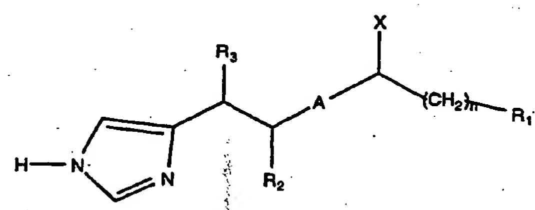
R_3 is hydrogen or a methyl or ethyl group;

n is 0, 1, 2, 3, 4, 5, or 6; and

R_1 is selected from the group consisting of (a) C_3 to C_8 cycloalkyl; (b) phenyl or substituted phenyl; (d) heterocyclic; (e) decahydronaphthalene and (f) octahydroindene; or

R_1 and X may be taken together to denote a 5,6 or 6,6 saturated bicyclic ring structure when X can be NH, O, or S.

Most preferably, the present invention provides compounds of the general formula:



(1.0)

where A is -CH=CH or $-C{\equiv}C-$;

X is H, CH_3 or NH_2;

R_2 and R_3 are H;

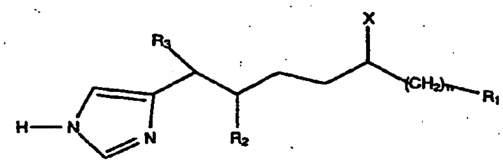
n is 1, 2, or 3;

R_1 is selected from the group consisting of (a) C_3 to C_8 cycloalkyl; (b) phenyl or substituted phenyl; (d) heterocyclic; (e) decahydronaphthalene and (f) octahydroindene; or

R_1 and X may be taken together to denote a 5,6 or 6,6 saturated bicyclic ring structure when X is NH, O, or S.

The pharmaceutically acceptable salts, hydrates and individual stereoisomers of compounds of structural formula (1.0) above, as well as mixtures thereof, are also contemplated as falling within the scope of the present invention.

Representative compounds of this invention include compounds of the formulae (2.0 through 11.0):



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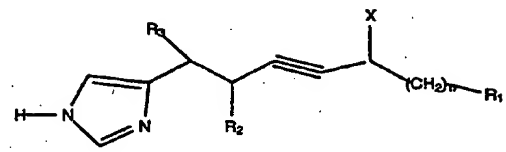

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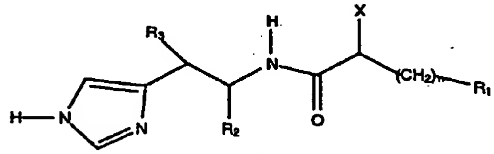

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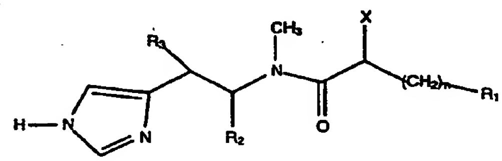

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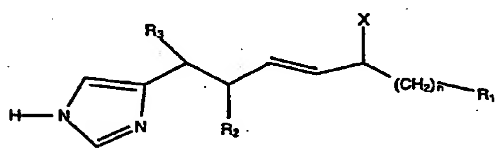

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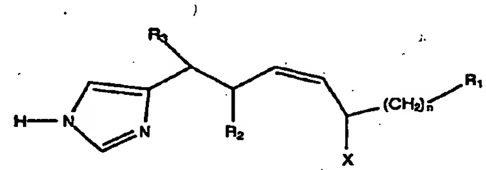

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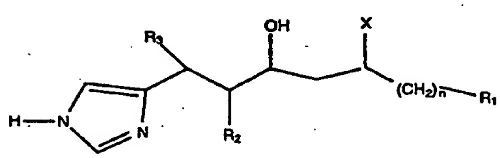

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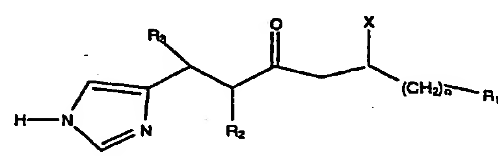

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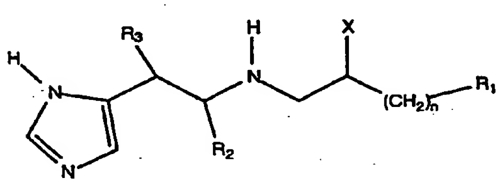
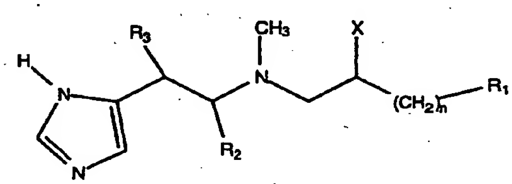
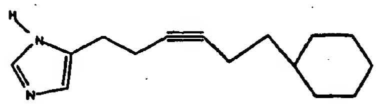


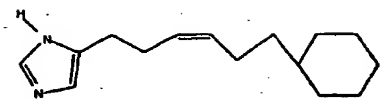
(10.0)

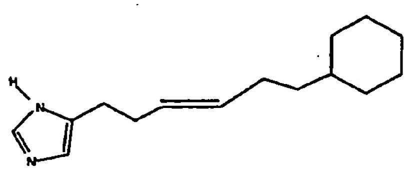


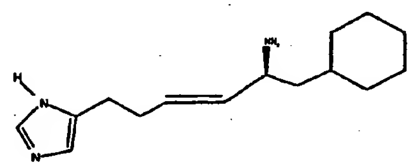
(11.0)

Particulary preferred compounds include:









Certain compounds of the invention may exist in different isomeric (e.g., enantiomers and diastereoisomers) forms. The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures. Enol forms are also included.

The compounds of formula (1.0) can exist in unhydrated as well as hydrated forms, e.g., hemi-hydrate, mono-, tetra-, decahydrates, etc. The water may be removed by heating or other means to form the anhydrous compound. In general, the hydrated forms, with pharmaceutically acceptable solvents such as water, ethanol, and the like are equivalent to the unhydrated forms for the purposes of the invention.

Certain compounds of the invention also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, the nitrogen atoms may form salts with acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous hydroxide, potassium carbonate, ammonia, and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid salts are equivalent to their respective free base forms for purposes of the invention. (See, for example S.M. Berge, et al.,"Pharmaceutical Salts," J. Pharm. Sci., 66: 1-19 (1977) which is incorporated herein by reference.

As throughout this specification and appended claims, the following t rms have the meanings ascribed to them:

The term "alkyl" as used herein refers to straight or branched chain radicals derived from saturated hydrocarbons by the removal of one hydrogen atom. Representative examples of alkyl groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, and the like.

The term "heterocyclic" as used herein refers to a closed-ring structure in which one or more of the atoms in the ring is an element other than carbon. Representative groups are preferably saturated and include pyrrolidines, tetrahydrofuranes, tetrahydrothiophenes, tetrahydroisoquinolines and octahydroindole groups.

The term "substituted phenyl" as used herein refers to a phenyl group substituted by one or more groups such as alkyl, halogen, amino, methoxy, and cyano groups.

Individual enantiomeric forms of compounds of the present invention can be separated from mixtures thereof by techniques well known in the art. For example, a mixture of diastereoisomeric salts may be formed by reacting the compounds of the present invention with an optically pure form of the acid, followed by purification of the mixture of diastereoisomers by recrystallization or chromatography and subsequent recovery of the resolved compound from the salt by basification. Alternatively, the optical isomers of the compounds of the present invention can be separated from one another by chromatographic techniques employing separation on an optically active chromatographic medium.

The present invention also provides pharmaceutical compositions which comprise one or more of the compounds of formula (1.0) above formulated together with one or more nontoxic pharmaceutically acceptable carriers. The pharmaceutical compositions may be specifically formulated for oral administration in solid or liquid form, parental injection, or for rectal administration.

The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically as by being within the scope of this invention.

Pharmaceutical compositions of this invention for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as perservatives, wetting agents and emulsifying agents.

In some cases, in order to prolong the effect of the drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium

phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylccllulos , alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hardfilled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredients(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, mulsifying and suspending agents, sweetening, flavoring, and p rfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum methydroxide, bentonite, agar-agar, and tragacanth, and mixtures thereof.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976) p.33 et seq.

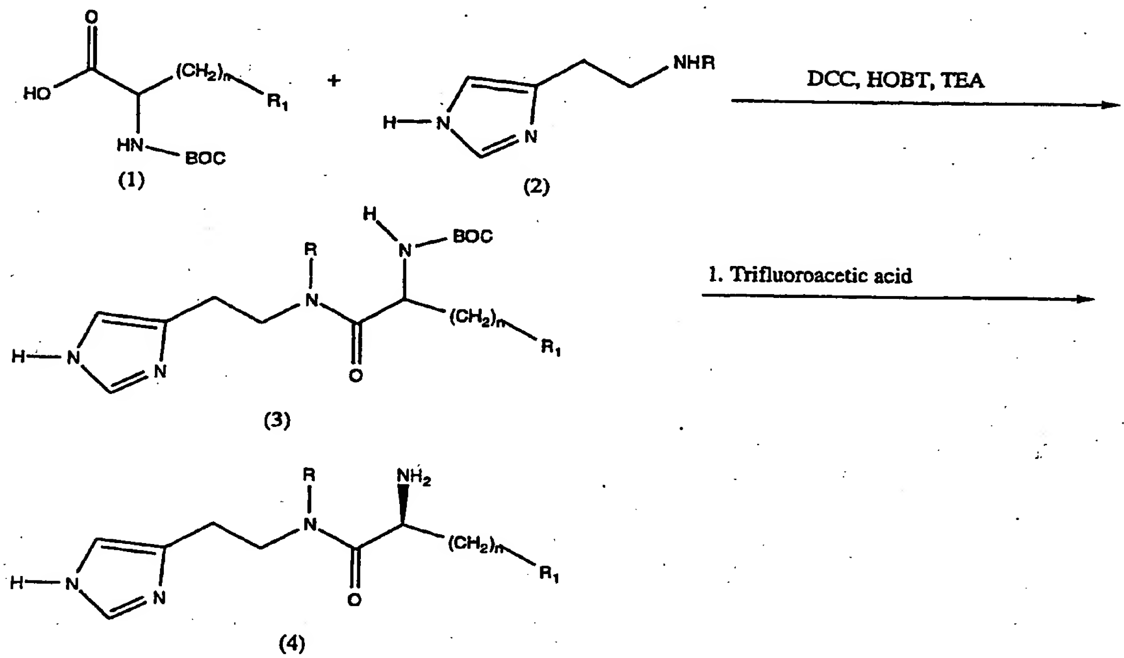
Dosage forms for topical administration of a compound of this invention include powders, sprays, ointments and inhalants. The active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers, or propellants which may be required. Opthalmic formulations, eye ointments, powders and solutions are also comtemplated as being within the scope of the invention.

The following processes and techniques may be employed to produce compounds of formula (1.0). The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformation being effected. It is understood by

those skilled in the art of organic synthesis that the functionality present in the molecul must be consistent with the chemical transformation proposed. This will fr quently necessitate judgement as to the order of synthetic steps, protecting groups required and deprotection conditions.

A. PREPARATION OF COMPOUNDS WHEREIN A IS -CONH- OR CONCH$_3$-

Scheme I

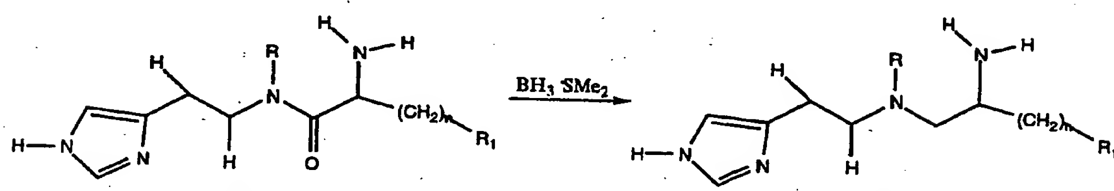


Scheme I

According to the foregoing reaction scheme I, the BOC protected amino acid (Natural configuration) 1 is reacted with histamine or N-Methyl histamine 2 under standard peptide coupling conditions using DCC and HOBT. After the reaction is complete (tlc or hplc analysis), the amide 3 is treated with trifluoroacetic acid or HCl in dioxane to remove the BOC group and provide the histamine or N-Methyl histamine amide 4.

B. PREPARATION OF COMPOUNDS WHEREIN A IS $-NHCH_2-$ OR $-N(CH_3)CH_2-$

Scheme II



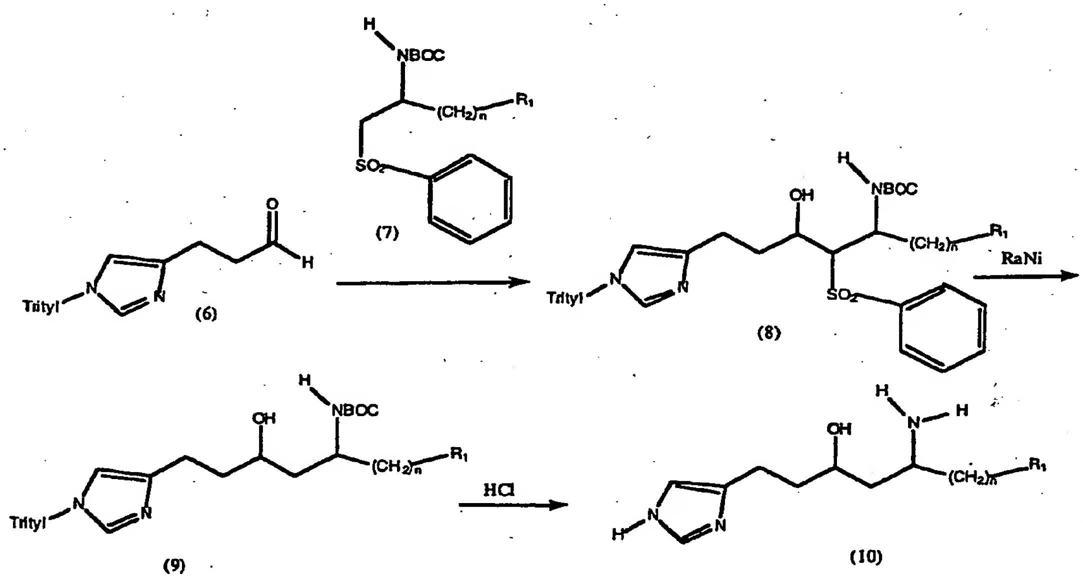
(4) (5)

Scheme II

According to the foregoing reaction scheme II, the histamine or N-methylhistaminecarboxamide (4), prepared as described in scheme I, is treated with excess borane-methyl sulfide complex to provide histamine or N-methylhistamine diamine (5).

C. PREPARATION OF COMPOUNDS WHEREIN A IS -CH(OH)CH_2-

Scheme III

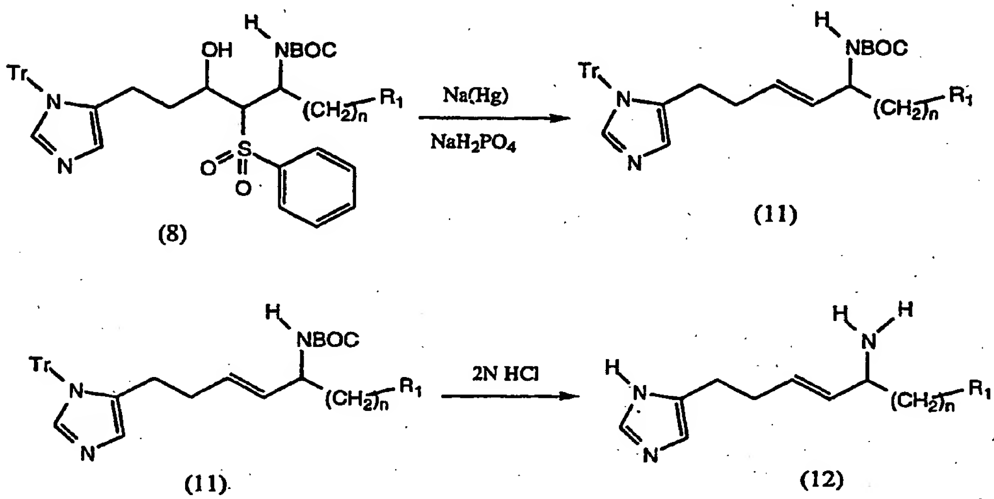


Scheme III

According to the foregoing reaction scheme III, 3-(1-Triphenylmethyl-5-imidazoyl)-propanal(6) is treated with the dianion of sulphone (7), prepared by the reaction of the sulphone with strong base,(n-BuLi) at -78°C. The diastereoisomeric mixture of beta hydroxy-sulphones (8) produced, is treated with excess Raney nickel (W - 2) at room temperature to give a mixture of alcohols (9). The Trityl protecting group is removed, as previously described, to provide the 1H-4(5)-imidazoyl-amino alcohols (10).

D. PREPARATION OF COMPOUNDS WHEREIN A IS -CH=CH-(Trans Olefins)

Scheme IV

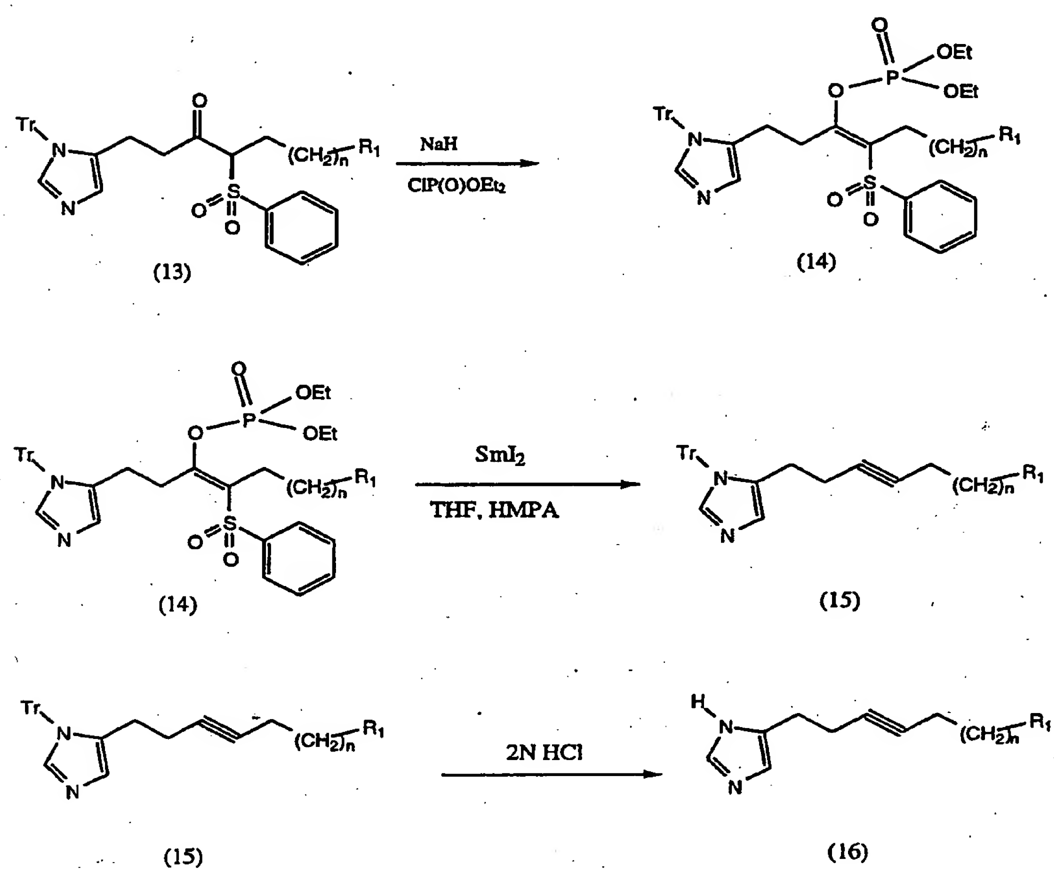


Scheme IV

According to the foregoing reaction scheme IV, the diastereoisomeric mixture of beta hydroxy sulphones (8) synthesized as described in scheme III, is treated with excess 2-3% Na(Hg) in methanol in the presence of 4 equivalents of sodium hydrogen phosphate buffer to provide the 3-(1-Triphenylmethyl-5-imidazoyl)trans olefin (11). Subsequent BOC deprotection and trityl deprotection with HCl gives 3-(1H-4(5)imidazoyl) trans olefin (12).

E. PREPARATION OF COMPOUNDS WHEREIN A IS —C≡C—

Scheme V

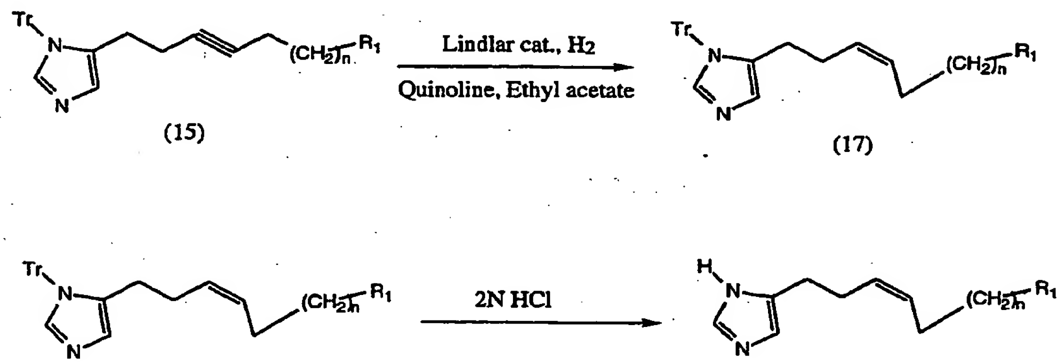


Scheme V

According to the foregoing reaction scheme V, the 3-(1-Triphenylmethyl-5-imidazoyl)-3-keto sulfone (13), is treated with NaH in THF, followed by reaction with diethyl chlorophosphate to give the enol phosphates (14). The enol phosphates are reduced with excess SmI_2 in dry THF and 4 mole % HMPA to provide the 3-(1-Triphenylmethyl-5-imidazoyl)-acetylene (15). Finally, deprotection of the trityl protecting group with HCl gives 3-(1H-5-imidazoyl)-acetylenes (16).

F. PREPARATION OF COMPOUNDS WHEREIN A IS -CH=CH-(Cis Olefins)

Scheme VI



(15) (17)

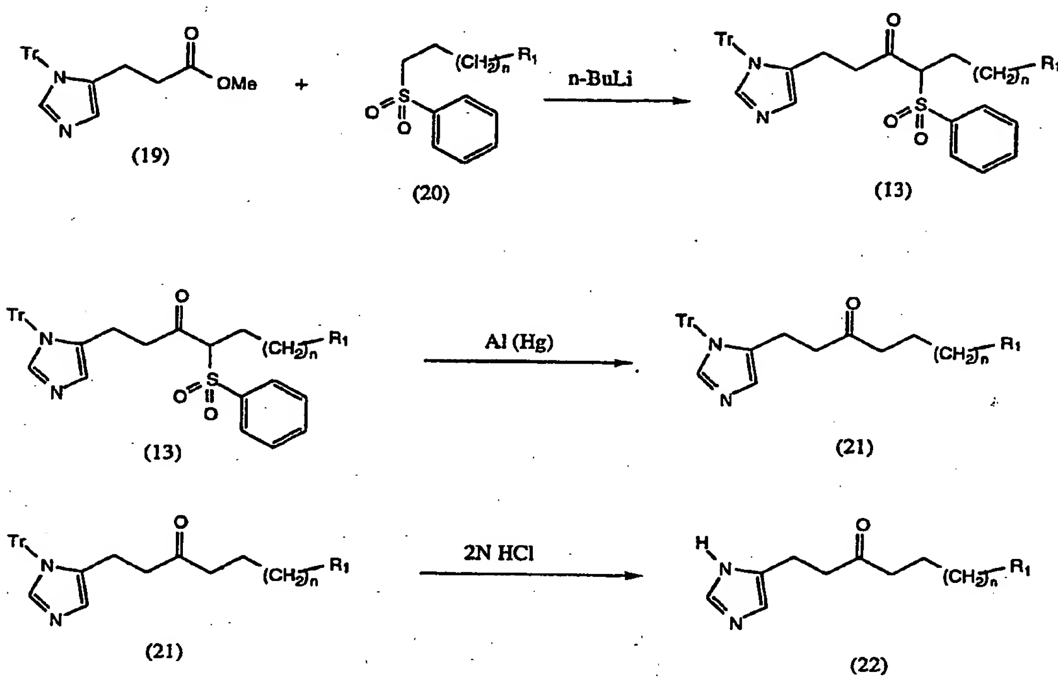
(17) (18)

Scheme VI

According to the foregoing reaction scheme VI, 3-(1-Triphenylmethyl-5-imidazoyl)-acetylene (15), prepared as in scheme V is hydrogenated with Lindlar catalyst to afford 3-(1-Triphenylmethyl-5-imidazoyl)-cis olefin (17). The Trityl group is deprotected with HCl to afford 3-(1H-5-imidazoyl)-cis olefin (18).

G. PREPARATION OF COMPOUNDS WHEREIN A IS -$COCH_2$-

Scheme VII

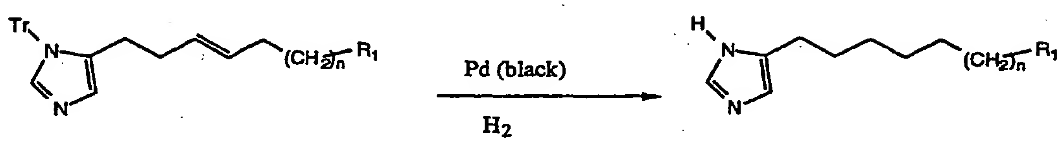


Scheme VII

According to the foregoing reaction scheme VII, condensation of the sulfone anion derived from (20) (treatment with n-BuLi at -78°C, 2.5 equivalents of sulfone: 1 equivalent of methyl ester) with the methyl ester (19) provides 3-(1-Triphenylmethyl-5-imidazoyl)-3-keto sulfone(13). Treatment of ketosulfone (13) with Al(Hg) gives 3 - (1-Triphenylmethyl-5-imidazoyl)-ketone (21). Trityl deprotection with HCl gives 3 - (1H-5-imidazoyl)ketone (22).

H. PREPARATION OF COMPOUNDS WHEREIN A IS $-CH_2CH_2-$

Scheme VIII



(15) (23)

Scheme VIII

According to the foregoing reaction scheme VIII, the 3-(1-Triphenylmethyl-5-imidazoyl)-trans olefin (15) is subjected to catalytic hydrogenation under the conditions described by Zervas et al., J. Am. Chem. Soc., 78, 1359 (1956), to reduce the carbon-carbon double bond and deprotect the trityl group, and provide the 5-(1H-5-imidazoyl)-amine (23).

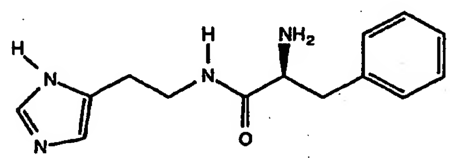
The present invention is further illustrated by the following representative examples.

EXAMPLE 1

Preparation of L-Phenylalanine-histamine amide

BOC-Phenylalanine (1.32g, 5 mM) was dissolved in 30 cc of dry THF and cooled to 0°C under N_2. N-Methyl Morpholine (0.66 ml, 6 mM) was added, followed by the dropwise addition of Isobutylchloroformate (0.65 ml, 5 mM). After 10 minutes at 0° C, histamine dihydrochloride (1.11 g, 6 mM) and triethylamine (1.68 ml, 12 mM) in 2 ml of THF/H_2O was added and the reaction mixture stirred for 2 hours. 5% $NaHCO_3$ solution was added, and the mixture was partioned between ethyl acetate and water 50 ml/50ml. The ethyl acetate layer was separated, washed with 5% $NaHCO_3$ solution, separated, dried over $MgSO_4$, filtered, and evaporated in vacuo to obtain the crude amino BOC protected L-Phenylalanine-histamine amide. The BOC group was removed directly by treatment with Trifluoroacetic acid (10 ml) for 30 minutes. TFA was evaporated and the residue triturated with ether and

the ditrifluoroacetic salt of L-Phenylalanine-histamine amid (1.20 grams) collected by filtration. Samples for the H_3 receptor binding assay was further purified by reverse phase HPLC.



Di-Trifluoroacetic acid salt

NMR (D_2O, 300 MHz): d 8.44 (s, 1H), 7.2 (m, 3H), 7.10 (m, 2H), 6.90 (s, 1H), 4.02 (AB q, 1H), 3.43 (m, 1H), 3.22 (m, 1H), 3.04 (dd, 1H), 2.94 (dd, 1H), 2.64 (m, 2H).

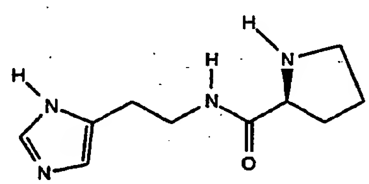
Mass Spectrum (+FAB): [259 $(M+1)^+$, 100%] MW= 258.3249, $C_{14}H_{18}N_4O$

Analytical HPLC: CH_3CN/H_2O/0.1% TFA; Gradient 20 ms, 20%; rt. 13.210 min.

EXAMPLE 2

Preparation of L-proline-histamine amide

L-proline-histamine amide was prepared as Example 1 except L-proline was used instead of L-Phenylalanine.



Di-Trifluoroacetic acid salt

NMR (D_2O, 300 MHz): d 8.44 (s, 1H), 7.16 (s, 1H), 4.20 (AB q, 1H), 3.52(m, 1H), 3.42 (m, 1H), 3.28 (m, 2H), 2.87 (m, 2H), 2.28 (m, 1H), 1.9 (m, 3H).

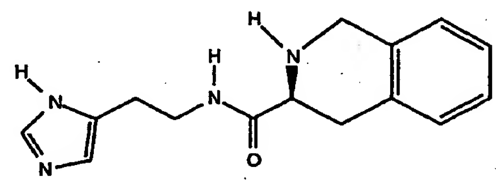
Mass Spectrum (+ FAB): [209 $(M+1)^+$, 100%] MW= 208.2649, $C_{10}H_{16}N_4O$

Analytical HPLC: CH_3CN/H_2O/ 0.1% TFA; Gradient 20 ms, 20%; rt. 7.0 min

EXAMPLE 3

Preparation of L-TIC-histamine amide

L-Tic-histamine amide was prepared as Example 1 except L-TIC was used.



Di-Trifluoroacetic acid salt

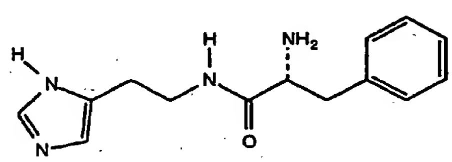
NMR (D_2O, 300 MHz): d 8.46 (s, 1H), 7.24 (m, 2H), 7.15 (m, 2H), 7.09 (s, 1H), 4.33 (AB q, 2H), 4.22 (m, 1H), 3.60 (m, 1H); 3.40 (m, 1H), 3.20 (dd, 1H), 3.02 (dd, 1H), 2.86 (m, 2H).

Mass Spectrum (+ FAB): [271 $(M+1)^+$, 100%] MW= 270.3359, $C_{15}H_{18}N_4O$.

EXAMPLE 4

Preparation of D-Phenylalanine-histamine amide

Phenylalanine-histamine amide was prepared in the same manner as Example 1 except D-Phenylalanine was used.



Di-Trifluoroacetic acid salt (D-Isomer)

NMR (D_2O, 300 MHz): d 8.44 (s, 1H), 7.20 (m, 3H), 7.10 (m, 2H), 6.90 (s, 1H), 4.02 (AB q, 1H), 3.43 (m, 1H), 3.22 (m, 1H), 3.04 (dd, 1H), 2.94 (dd, 1H), 2.64 (m, 2H).

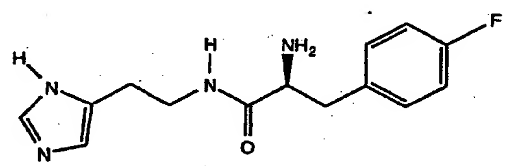
Mass Spectrum (+FAB): [259 $(M+1)^+$, 100%] MW= 258.3249, $C_{14}H_{18}N_4O$

Analytical HPLC: CH_3CN/H_2O/0.1% TFA; Gradient 20 ms, 20%; rt. 13.21 min.

EXAMPLE 5

Preparation of L-p-Fluorophenylalanine-histamine amide

L-p-Fluorophenylalanine-histamine amide was prepared in the same manner as Example 1, except L-p-Fluorophenylalanine was used.



Di-Trifluoroacetic acid salt

NMR (D_2O, 300 mHz): d 8.46 (s, 1H), 7.09 (m, 2H), 6.95 (m, 3H), 4.00 (dd, 1H), 3.46 (m, 1H), 3.26 (m, 1H), 3.06 (dd, 1H), 2.94 (dd, 1H), 2.68

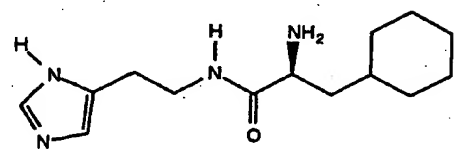
Mass Spectrum (+ FAB): [277 $(M+1)^+$, 100%] MW= 276.3153, $C_{14}H_{17}N_4O_1F_1$

Analytical HPLC: CH_3CN/H_2O/ 0.1% TFA; Gradient 20 ms, 20%; rt. 14.25 min

EXAMPLE 6

Preparation of L-Cyclohexylalanine-histamine amide

L-Cyclohexylalanine-histamine amide was prepared in the same manner as Example 1, except L-Cyclohexylalanine was used.



Di-Trifluoroacetic acid salt

NMR (D_2O, 300 MHz): d 8.56(s, 1H), 7.20 (s, 1H), 3.82 (m, 1H), 3.65 (m, 1H), 3.45 (m, 1H), 3.34 (m, 1H), 2.88 (m, 2H), 1.5 (m, 6H), 1.0 (m, 4H), 0.80 (m, 1H).

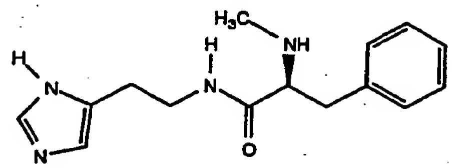
Mass Spectrum (+FAB): [265 $(M+1)^+$, 100%] MW= 264.3729, $C_{14}H_{24}N_4O_1$

Analytical HPLC: CH_3CN/H_2O/0.1% TFA; Gradient: 20 ms, 20%; rt. 17.326 min

EXAMPLE 7

Preparation of L-N-Methylphenylalanine-histamine amide

L-N-Methylphenylalanine-histamine amide was prepared in the same manner as Example 1, except L-N-Methylphenylalanine was used.



Di-Trifluoroacetic acid salt

NMR (D_2O, 300 MHz): d 8.44 (s, 1H), 7.20 (m, 3H), 7.10 (m, 2H), 6.86 (s, 1H), 3.92 (m, 1H), 3.42 (m, 1H), 3.20 (m, 2H), 2.94 (dd, 1H), 2.62 (m, 2H), 2.57 (s, 3H).

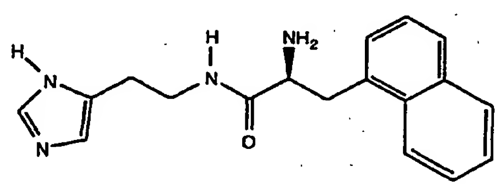
Mass Spectrum (+FAB): [273 $(M+1)^+$, 100%] MW=272.3519, $C_{15}H_{20}N_4O_1$.

Analytical HPLC: CH_3CN/H_2O/ 0.1% TFA; Gradient 20 ms, 20%; rt. (prep only)

EXAMPLE 8

Preparation of L-3-(2'-Naphthyl)-alanine-histamine amide

L-3-(2'-Naphthyl)-alanine-histamine amide was prepared in the same manner as Example 1 except L-3-(2'-Naphthyl)-alanine was used.



Di-Trifluoroacetic acid salt

NMR (D_2O, 300 MHz): d 8.4 (s, 1H), 7.91 (d, 1H), 7.82 (d, 1H), 7.72 (d, 1H), 7.5 (m, 2H), 7.33 (m, 2H), 6.5 (s, 1H), 4.16 (m, 1H), 3.5 (m, 2H), 3.22 (m, 1H), 2.96 (m, 1H), 2.24 (m, 2H).

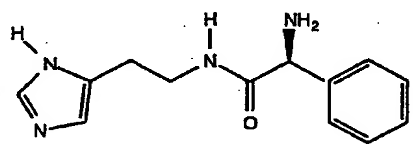
Mass Spectrum (+FAB): [309 $(M+1)^+$, 100%] MW= 308.3849, $C_{18}H_{20}N_4O_1$.

Analytical HPLC: CH_3CN/H_2O/ 0.1% TFA; Gradient 20 ms, 20%; 25 ms, 90%; rt. 20.99 min.

EXAMPLE 9

Preparation of L-2-Phenylglycine-histamine amide

L-2-Phenylglycine-histamine amide was prepared in the same manner as Example 1 except L-2-Phenylglycine was used.



Di-Trifluoroacetic acid salt

NMR (D_2O, 300 MHz): d 8.38 (s, 1H), 7.41 (m, 3H), 7.24 (m, 2H), 6.6 (s, 1H), 3.7 (m, 1H), 3.25 (m, 1H), 3.19 (m, 1H), 2.8 (m, 1H), 2.7 (m, 1H).

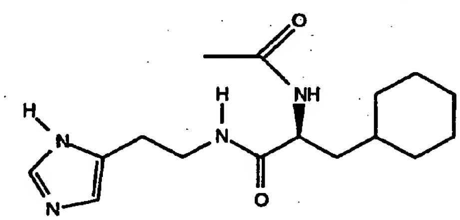
Mass Spectrum (+FAB): [245 $(M+1)^+$, 100%] MW= 244.2979, $C_{13}H_{16}N_4O_1$.

Analytical HPLC: CH_3CN/H_2O/ 0.1% TFA; Gradient 20 ms, 20%; rt. 10.08 min.

EXAMPLE 10

Preparation of L-N-Acetylphenylalanine-histamine amide

L-N-Acetylphenylalanine-histamine amide was prepared in the same manner as Example 1 except L-N-Acetylphenylalanine was used and no BOC deprotection step was necessary.



Trifluoroacetic acid salt

NMR (D_2O, 300 MHz): d 8.49 (s, 1H), 7.17 (s, 1H), 4.06 (dd, 1H), 3.40 (m, 2H),
2.83 (t, 2H), 1.90 (s, 3H), 1.52 (m, 6H), 1.36 (m, 1H), 1.04 (m, 4H), 0.78 (m, 2H).

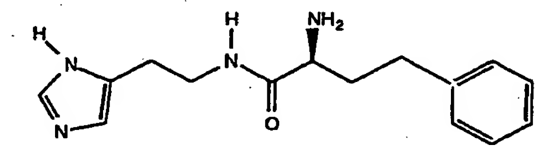
Mass Spectrum (+FAB): [307 $(M+1)^+$, 100%] MW= 306.4109, $C_{16}H_{26}N_4O_2$.

Analytical HPLC: CH_3CN/H_2O/ 0.1% TFA; Gradient 20 ms, 20%; rt. (prep only)

EXAMPLE 11

Preparation of L-Homophenylalanine-histamine amide

L-Homophenylalanine-histamine amide was prepared in the same manner as Example 1 except L-Homophenylalanine was used.



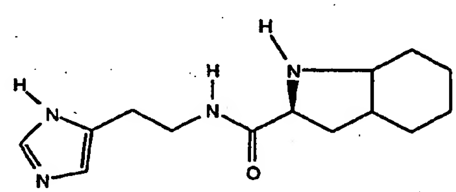
Di-Trifluoroacetic acid salt

NMR (D_2O, 300 MHz): d 8.42 (s, 1H), 7.19 (m, 6H), 3.85 (m, 1H), 3.52 (m, 1H), 3.35 (m, 1H), 2.82 (m, 2H), 2.46 (m, 2H), 2.00 (m, 2H).
Mass Spectrum (+FAB): [273 $(M+1)^+$, 100%] MW= 272.3518, $C_{15}H_{20}N_4O_1$.
Analytical HPLC: CH_3CN/H_2O/ 0.1% TFA; Gradient 20 ms, 20%; rt. (prep only)

EXAMPLE 12

Preparation of L-OIC-histamine amide

L-OIC-histamine amide was prepared in the same manner as Example 1 except L-OIC was used.



Di-Trifluoroacetic acid salt

NMR (D_2O, 300 MHz): d 8.54 (s, 1H), 7.18 (s, 1H), 4.26 (m, 1H), 3.65 (m, 2H), 3.4 (m, 1H), 2.87 (m, 2H), 2.32 (m, 2H), 1.92 (m, 1H), 1.75 (m, 2H), 1.58-1.20 (m, 6H).

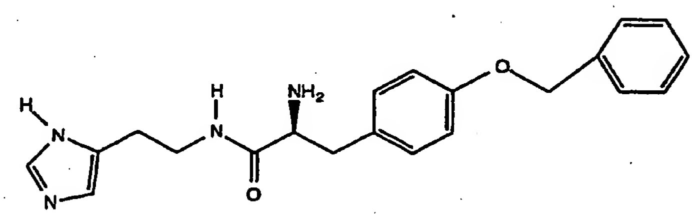
Mass Spectrum (+FAB): [263 $(M+1)^+$, 100%] MW= 262.3569, $C_{14}H_{22}N_4O_1$.

Analytical HPLC: CH_3CN/H_2O/0.1% TFA; Gradient 20 ms, 20%, 30 ms, 100%, 35 ms 100 %; rt. 13.160.

EXAMPLE 13

Preparation of O-Benzyl-L-Tyrosine-histamine amide

O-Benzyl-L-Tyrosine-histamine amide was prepared in the same manner as Example 1 except N-BOC-O-Benzyl-L-Tyrosine was used.



Di-Trifluoroacetic acid salt

NMR (D_2O, 300 MHz): d 8.42 (s, 1H), 7.3 (m, 5H), 7.02 (d, 2H), 6.86 (m, 3H), 5.1 (s, 2H), 3.97 (dd, 1H), 3.44 (m, 2H), 3.18 (m, 1H), 3.02 (dd, 1H), 2.90 (m, 1H), 2.55 (m, 1H).

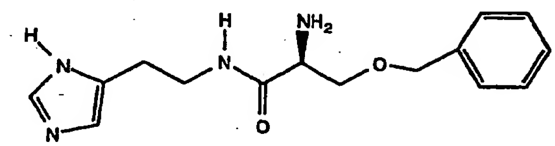
Mass Spectrum (+FAB): [365 $(M+1)^+$, 100%] MW= 364.4499, $C_{21}H_{24}N_4O_2$.

Analytical HPLC: CH_3CN/H_2O/0.1% TFA; Gradient 20ms, 20%; rt. 30.08 min.

EXAMPLE 14

Preparation of O-Benzyl-L-Serine-histamine amide

O-Benzyl-L-Serine-histamine amide was prepared in the same manner as Example 1, except N-BOC-O-Benzyl-L-Serine was used.



Di-Trifluoroacetic acid salt

NMR (D_2O, 300 MHz): d 8.38 (s, 1H), 7.32 (m, 3H), 7.25 (m, 2H), 7.05 (s,1H), 4.45 (AB q, 2H), 4.07 (m, 1H), 3.7 (m, 2H), 3.48 (m, 1H), 3.37 (m, 1H), 2.8 (m, 2H).

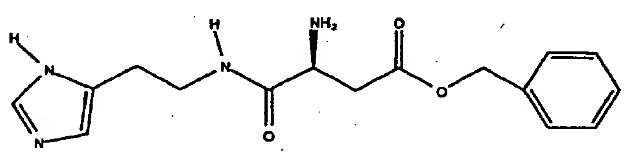
Mass Spectrum (+FAB): [289 $(M+1)^+$, 100%] MW= 288.3518, $C_{15}H_{20}N_4O_2$.

Analytical HPLC: CH_3CN/H_2O/0.1% TFA; Gradient 20 ms, 20%, 25 ms, 100%; rt. 12.14 min.

EXAMPLE 15

Preparation of L-Aspartic acid B-benzyl ester-histamine amide

L-Aspartic acid B-benzyl ester-histamine amide was prepared in the same manner as Example 1, except N-BOC-L-Aspartic acid B-Benzyl ester was used.



Di-Trifluoroacetic acid salt

NMR (D_2O, 300 MHz): d 8.40 (s, 1H), 7.35 (m, 5H), 7.05 (s, 1H), 5.10 (s, 2H), 4.19 (m, 1H), 3.4 (m, 1H), 3.3 (m, 1H), 2.94 (m, 2H), 2.7 (m, 2H).

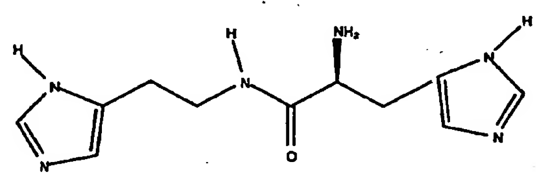
Mass Spectrum (+FAB): [317 $(M+1)^+$, 100%] MW= 316.3629, $C_{16}H_{20}N_4O_3$.

Analytical HPLC: CH_3CN/H_2O/0.1% TFA; Gradient 20 ms, 20%, 25 ms, 100 %; rt. 13.80 min.

EXAMPLE 16

Preparation of L-Histidine-histamine amide

L-Histidine-histamine amide was prepared in the same manner as Example 1 except N-BOC-L-Histidine was used.



Tri-Trifluoroacetic acid salt

NMR (D_2O, 300 MHz): d 8.54 (s, 1H), 8.50(s, 1H), 7.28 (s, 1H), 7.14 (s,1H), 4.11 (m, 1H), 3.43 (m, 4H), 3.22 (d, 2H), 2.80 (m, 4H).

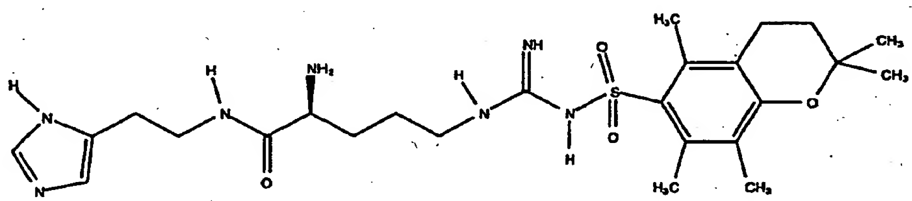
Mass Spectrum (+FAB): [249 $(M+1)^+$, 100%] MW= 248.2894, $C_{11}H_{16}N_6O_1$.

Analytical HPLC: CH_3CN/H_2O/0.1% TFA; Gradient: 1nn, 0%, 5ms, opc, 15 ms, 10%, 20 ms, 100%; rt. 6.65 min.

EXAMPLE 17

Preparation of N-PMC-L-Arginine-histamine amide

N-α-FMOC-N-PMC-L-Arginine (0.66 g, 1mM) was dissolved in 20 ml of dry THF and cooled to 0°C under N_2. N-Methyl morpholine (0.11 ml, 1 mM) was added, followed by Isobutylchloroformate (0.13 ml, 1 mM). After 10 minutes, histamine dihydrochloride (0.37 g, 2 mM) and triethylamine (0.56 ml,4 mM) in 2 ml of water was added. After 1 hour the reaction mixture was partioned between ethyl acetate and water (50 ml/50 ml), and washed with 5% $NaHCO_3$. The ethyl acetate layer was separated, dried over $MgSO_4$, filtered, and evaporated to provide crude N-α-FMOC-N-PMC-L-Arginine-histamine amide. The FMOC group was cleaved by treatment with DEA in THF (10 ml) for 4 hours. The reaction mixture was evaporated to dryness, the solid filtered, and washed with ether (3X 50 ml) to give N-PMC-L-Arginine-histamine amide (500 mg). A sample for in-vitro testing was further purified by reverse phase HPLC.



Di-Trifluoroacetic acid salt

NMR (D_2O, 300 MHz): d 8.5 (s, 1H), 7.04 (s, 1H), 3.81 (m, 1H), 3.5 (m, 1H), 3.35 (m, 1H), 3.09 (m, 2H), 2.8 (m, 2H), 2.57 (m, 2H), 2.42 (s, 3H), 2.39 (s, 3H), 2.00 (s, 3H), 1.73 (m, 2H), 1.67 (m, 2H), 1.37 (m, 2H).

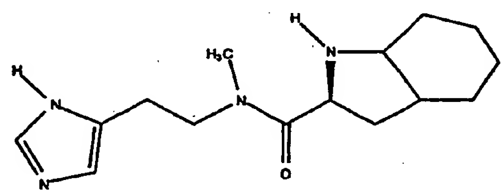
Mass Spectrum (+FAB): [534 $(M+1)^+$, 100%] MW= 533.7001, $C_{25}H_{39}N_7O_4S_1$

Analytical HPLC: CH_3CN/H_2O/0.1% TFA; Gradient: 1nn, 20%, 20 ms, 40%, 25 ms, 100%, 30 ms, 20 %; rt. 15.07 min.

EXAMPLE 18

Preparation of L-OIC-N-Methylhistamine amide

N-Methylhistamine dihydrochloride (100 mg, 0.5 mM) dissolved in THF/DMSO (4:1 ml) and a few drops of water was neutralized with triethylamine (0.14 ml, 1 mM). To N-BOC-L-OIC (0.27 g, 1 mM) dissolved in 5 ml of THF was added HOBT (0.30 g, 2 mM) followed by DIC (0.126 g, 1mM). After 10 minutes this mixture was added with stirring to the solution of N-Methylhistamine, and the reaction was stirred overnight. The mixture was diluted with ethyl acetate/water (50 ml). The organic layer was separated, washed with 5% $NaHCO_3$, saturated NaCl solution, dried over $MgSO_4$, and evaporated to dryness. The crude N-BOC- L-OIC-N-Methylhistamine amide was deprotected by treatment with trifluoroacetic acid (10 ml) for 45 minutes. The TFA was evaporated, and the residue repeatedly washed with methanol. Purification of the crude residue by reverse phase HPLC, gave after freeze drying 100 mg of L-OIC-N-Methylhistamine amide ditrifluoroacetic acid salt.



Di-Trifluoroacetic acid salt

NMR (D_2O, 300 MHz): d 8.58 (s, 1H), 7.22 (s, 1H), 4.58 (m, 1H), 3.98 (m, 1H), 3.70 (m, 1H), 3.26 (m, 1H), 2.95 (s, 3H), 2.94 (m, 2H), 2.5 (m, 1H), 2.30 (m, 1H), 1.86-1.00 (m, 9H).

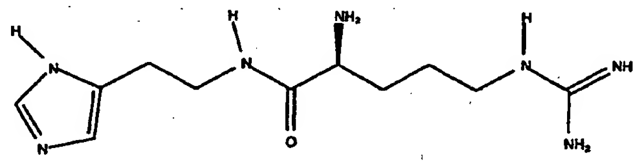
Mass Spectrum (+FAB): [277 $(M+1)^+$, 100%] MW= 276.3839, $C_{15}H_{24}N_4O_1$

Analytical HPLC: CH_3CN/H_2O/ 0.1% TFA; Gradient: (Prep col): 1nn, 0%, 20 ms, 40%, 25 ms, 100%; rt. 11.891 min.

EXAMPLE 19

Preparation of L-Arginine-histamine amide

N-PMC-L-Arginine-histamine amide (150 mg), prepared as in Example 17 was treated with Trifluoroacetic acid -phenol (9:1) solution (5 ml) for two hours. Trifluoroacetic acid was evaporated and the residue triturated with ether (3X 50 ml). The ether was decanted, and the residue dissolved in water and purified by HPLC to afford 90 mgs of L-Arginine-histamine amide.



Di-Trifluoroacetic acid salt

NMR (D_2O, 300 MHz): d 8.50 (s, 1H), 7.19 (s, 1H), 3.48 (m, 2H), 3.09 (m, 2H), 2.87 (m, 2H), 1.75 (m, 2H), 1.45 (m, 2H).

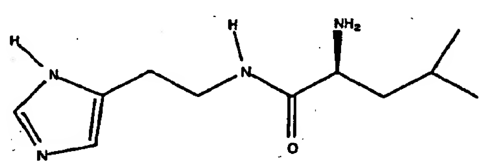
Mass Spectrum (+FAB): [268 $(M+1)^+$, 100%] MW= 267.3361, $C_{11}H_{21}N_7O_1$.

Analytical HPLC: CH_3CN/H_2O/0.1% TFA; Gradient: 1nn, 0%, 20 ms, 20%, 25 ms, 100%; rt. 4.63 min.

EXAMPLE 20

Preparation of L-Leucine-histamine amide

L-Leucine-histamine amide was prepared in the same manner as Example 1 except N-BOC-L-leucine was used.



Di-Trifluoroacetic acid salt

NMR (D_2O, 300 MHz): d 8.5 (s, 1H), 7.2 (s, 1H), 3.78 (m, 1H), 3.65 (m, 1H), 3.35 (m, 1H), 2.88 (m, 2H), 1.50 (m, 2H), 1.26 (m, 1H), 0.79 (d, 6H).

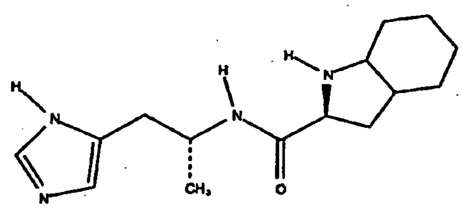
Mass Spectrum: (+FAB): [225 $(M+1)^+$, 100 %] MW= 224.3079, $C_{11}H_{20}N_4O_1$.

Analytical HPLC: CH_3CN/H_2O/0.1% TFA; Gradient: 1nn, 0%, 15 ms, 15%, 20 ms, 100%; rt. 10.21 min.

EXAMPLE 21

Preparation of L-OIC-a-methy-histamine amide

N-BOC-L-OIC (0.269 g, 1 mM), HOBT (0.150 g, 1mM), and DIC (0.126 g, 1 mM) was dissolved in 5 ml of THF. After 10 minutes, the N-BOC-L-OIC HOBT ester was added to a solution of α-Methylhistamine dihydrochloride (0.100 g, 0.5 mM) and triethylamine (0.14 ml, 1 mM) in 5 ml of isopropanol. The reaction mixture was stirred for 18 hours at r.t. and then partioned between ethyl acetate and water (50 ml). The ethyl acetate layer was separated, washed with 5% $NaHCO_3$, water, dried over $MgSO_4$. After evaporation in vacuo, the BOC group was removed by treatment with Trifluoroacetic acid (5 ml) for 30 minutes, and the crude product purified by HPLC chromatography to afford 70 mgs of L-OIC-α-methy-histamine amide.



Di-Trifluoroacetic acid salt

NMR (D_2O, 300 MHz): d 8.51 (s, 1H), 7.2 (s, 1H), 4.24 (m, 1H), 4.11 (m, 1H), 3.72 (m, 1H), 2.86 (m, 2H), 2.36 (m, 2H), 2.18-1.22 (m, 9H), 1.14 (d, 3H).

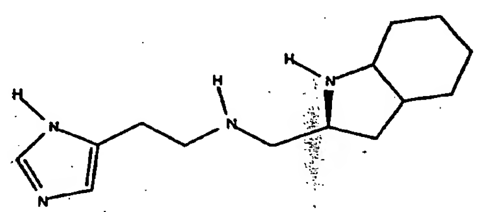
Mass Spectrum (+FAB): [277 $(M+1)^+$, 100%] MW= 276.3839, $C_{15}H_{24}N_4O_1$.

Analytical HPLC: CH_3CN/H_2O/0.1% TFA; Gradient: 1nn, 0%, 20 ms,20%, 25 ms, 100%; rt. 17.32 min.

EXAMPLE 22

Preparation of Reduced L-OIC-histamine amide

N-BOC-L-OIC-histamine amide (0.140 g, 0.396 mM) prepared as in Example 12, was dissolved in 10 ml of dry THF and heated to 60°C under N_2. $BH_3(SMe_2)$, (0.237 ml, 6 equivalents) was added dropwise to the solution and the reaction stirred for 30 minutes. The reaction was cooled, TMEDA (0.068g) was added, the reaction mixture stirred for additional hour, and then the organic volatiles removed on rotary evaporator. To the crude residue was added Trifluoroacetic acid (5 ml), and the reaction stirred for 30 minutes. TFA was evaporated and the crude purified by reverse phase HPLC to give 40 mgs of the reduced L-OIC-histamine amide.

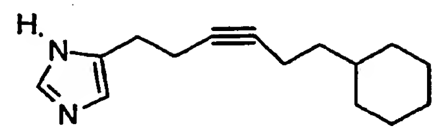


Tri-Trifluoroacetic acid salt

NMR (D_2O, 300 MHz): d 8.54 (s, 1H), 7.18 (s, 1H), 4.06 (m, 1H), 3.45 (m, 2H), 3.4 (m, 1H), 3.35 (m,2H), 2.87 (m, 2H), 2.32 (m, 2H), 1.92 (m, 1H), 1.75 (m, 2H), 1.58-1.20 (m, 6H).

Mass Spectrum (+FAB): [249 $(M+1)^+$, 100%] MW= 248.3729, $C_{14}H_{24}N_4$.

EXAMPLE 23



Preparation of 1-[(1H)-5-imidazoyl]- 6-cyclohexyl-3-hexyne

Step 1

3-cyclohexylpropyl-p-toluene sulfone (32.2 grams, 0.115 moles) was dissolved in 500cc of dry THF and cooled to -78°C under N_2. n-BuLi (2.5M in hexanes, 50.6 ml, 0.126 moles) was added dropwise via syringe, and the reaction mixture stirred at -78°C for 30 minutes. 3-[1-Triphenylmethyl-5-imidazoyl]-methyl propanoate (20 grams, 50 mmoles) was dissolved in 150 cc of dry THF and cooled to -78°C under N_2. The sulfone anion solution was added to the THF solution of methyl ester via cannula (approximately 20 minutes), and the reaction mixture stirred for 1 hour after the addition was complete. The reaction was quenched by the addition of 500 cc of a saturated solution of ammonium chloride, and extracted with ethyl acetate (2X 300 cc). The ethyl acetate layer was separated, dried over $MgSO_4$, filtered, and evaporated in vacuo to afford a viscous yellow oil. The crude product was purified by silica gel column chromatography using ethyl acetate/hexanes to afford 32 grams of a white solid, the racemic mixture of 1-[1-Triphenylmethyl -5-imidazoyl]- 4-p-toluenesulfonyl-6-cyclohexyl hexan-3-one.

NMR ($CDCl_3$, 300 Mhz): d 7.60 (d, 2H, J=8 Hz), 7.30 (m, 9H), 7.26 (d, 2H, J=8 Hz), 7.10 (m, 7H), 6.56 (s, 1H), 4.04 (dd, 1H, J=4.6 Hz), 3.14 (m, 1H), 2.97 (m, 1H), 2.78 (m, 2H), 2.40 (s, 3H), 1.82 (m, 2H), 1.56 (m, 6H), 1.07 (m, 5H), 0.72 (m, 2H).

Mass Spectrum (DCI/NH_3): 645 (M+1), MW= 644.8824, $C_{41} H_{44} N_2 S_1 O_3$

Step 2

NaH (60% dispersion in mineral oil, 4.65 grams, 0.116 moles) was suspended in dry THF (300 cc) and 54 cc of HMPA at 0°C under N_2. 1-[1-Triphenylmethyl-5-imidazoyl] -4-p-toluenesulfonyl-6-cyclohexyl hexan-3-one (60 grams, 0.093 moles) in 150 cc of dry THF was added via cannula to the NaH suspension. The reaction mixture was stirred for 30 minutes after the addition was complete. Diethyl chlorophosphate (16.15 cc, 0.112 moles) was added via syringe, and the reaction mixture left to stir at r.t. for 24 hours. The reaction was quenched by the addition of 500 cc of a saturated solution of ammonium chloride, and extracted with 2X 500 cc of ethyl acetate. The ethyl acetate layer was separated, washed with 2X 500 cc of water, followed by washing with 2X 500 cc of brine. The ethyl acetate layer was dried over $MgSO_4$, filtered, and evaporated in vacuo to afford a viscous yellow oil. The crude oil was purified by passing through a pad of silica gel (200 grams) using approximately 1.5 liters of ethyl acetate/hexanes 2:8. The ethyl acetate/hexanes filtrate was evaporated in vacuo, and the solid remaining was triturated with dry ether (150 cc), filtered and washed with ether to give 33 grams of a crystalline white solid (first crop). The filtrate was once again evaporated in vacuo to give additional solid which again was triturated with ether to give after filtration 11.27 grams of white solid (second crop). Repeating this sequence one more time gave an additional 3.88 grams for a combined total of 48.15 grams (67%) of white solid, 1-[1-Triphenylmethyl -5-imidazoyl] -3-(diethoxyl phosphinyl) oxy-4-p-toluenesulfonyl-6-cyclohexyl 3-hexene.

NMR ($CDCl_3$, 300 Mhz): d 7.72 (d, 2H, J=7 Hz), 7.30 (m, 9H), 7.14 (d, 2H, J=7 Hz), 7.08 (m, 7H), 6.47 (s, 1H), 4.14 (Overlapping quartets, 4H), 2.74 (m, 4H), 2.34 (s, 3H), 2.26 (m, 2H), 1.64 (m, 5H), 1.40-1.02 (m, 6H), 1.26 (t, 6H), 0.86 (m, 2H).

Step 3

1-[1-Triphenylmethyl-5-imidazoyl]-3-(diethoxyphosphinyl)oxy-4-p-toluenesulfonyl-6-cyclohexyl-3-hexene (14.5 grams, 0.018 moles) was dissolved in 150 cc of dry THF and 10 cc of HMPA at r.t. under N_2. SmI_2 (0.1M solution in THF) was added to the reaction in 50 ml portions via syringe. A total of 400 cc of 0.1M SmI_2 was added. After the last 50 ml portion was added, the blue reaction mixture was stirred for 1 hour. The reaction mixture was added to 500 cc of a saturated solution of ammonium chloride, and extracted with ethyl acetate (2X 500 cc). The ethyl acetate layer was washed with brine (250 cc), water (2X 400 cc), and brine (250 cc). The ethyl acetate layer was separated, dried over $MgSO_4$, filtered, and evaporated in vacuo to give a yellow oil. The crude acetylene was taken up in 25 cc of $CHCl_3$ and filtered through a pad of silica gel (200 grams) using 1 liter of ethyl acetate/hexanes (2:8). The filtrate was evaporated in vacuo to afford a viscous yellow oil which solidified upon standing. The solid was triturated with hexanes, filtered, and washed with hexanes to give 5.5 grams of 1-[1-Triphenylmethyl-5-imidazoyl]-6-cyclohexyl-3-hexyne.

NMR ($CDCl_3$, 300 Mhz): d 7.30 (m, 9H), 7.12 (m, 7H), 6.60 (m, 1H), 2.70 (m, 2H), 2.42 (m, 2H), 2.06 (m, 2H), 1.64 (m, 5H), 1.34 - 1.04 (m, 6H), 0.82 (m, 2H).

Mass Spectrum (DCI/NH_3): 473 $(M+1)^+$, MW= 472.6754, $C_{34}H_{36}N_2$

CHN: Calc.: C: 86.39, H: 7.67, N: 5.92; Found: C: 85.82, H: 7.73, N: 5.79.

Step 4

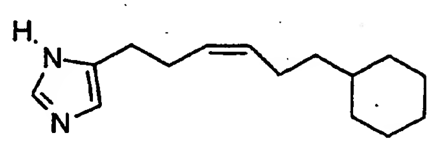
1-[1-Triphenylmethyl-5-imidazoyl]-6-cyclohexyl-3-hexyne (0.30 gram, 0.64 mM) was dissolved in 10 cc of ethanol. 20 cc of 2N HCl was added, and the mixture heated at 90°C for 1 hour. The reaction mixture was cooled, filtered, and the filtrate neutralized with 10% NaOH solution, and then partitioned between chloroform and water. The chloroform layer was separated, dried over Na_2SO_4, filtered, and evaporated in vacuo to obtain the crude oil. The crude product was purified using column chromatography using $MeOH/CHCl_3$, 10:90 to afford 155 mgs of 1-[1(H)-5-imidazoyl]-6-cyclohexyl-3-hexyne.

NMR ($CDCl_3$, 300 Mhz): d 7.05 (s, 1H), 6.83 (s, 1H), 2.80 (m, 2H), 2.45 (m, 2H), 2,15 (m, 2H), 1.68 (m, 5H), 1.4 - 1.1 (m, 6H), 0.86 (m, 2H).

Mass Spectrum: (DCI/NH_3): 231 $(M+1)^+$, MW= 230.3434, $C_{15}H_{22}N_2$.

CHN Analysis: Calc.: C: 78.26, H: 9.56, N: 12.17; Found: C: 77.79, H: 9.51, N: 11.86.

EXAMPLE 24



Preparation of 1-[1(H)-5-imidazoyl]-6-cyclohexyl-cis-3-hexene

Step 1

1-[1-Triphenylmethyl-5-imidazoyl]-6-cyclohexyl-3-hexyne (6.8 grams, 0.014 moles) was dissolved in 100 ml of dry ethyl acetate. 1.8 grams of 5% Lindlar catalyst (Pd on $CaCO_3$ poisoned with lead) and 15 mgs of quinoline were added. H_2 was added to the reaction flask via a balloon apparatus. The reaction flask was evacuated and then refilled with H_2 gas from the balloon 3 times. The reaction was left to stir at r.t. under the presence of H_2 (1 atm) for 48 hours. The H_2 gas was removed, and the reaction mixture filtered through a pad of celite with ethyl acetate, the ethyl acetate was removed in vacuo to afford 6.75 grams of 1-[1-Triphenylmethyl-5-imidazoyl]-6-cyclohexyl-cis-3-hexene.

NMR ($CDCl_3$, 300 MHz): d 7.30 (m, 9H), 7.12 (m, 7H), 6.50 (s, 1H), 5.31 (m,2H), 2.57 (m, 2H), 2.34 (m, 2H), 1.96 (m, 2H), 1.64 (m,5H), 1.50 (m, 6H), 0.82 (m, 2H).

Mass Spectrum: (DCI/NH_3): 475 $(M+1)^+$, MW= 474.6914, $C_{34}H_{38}N_2$

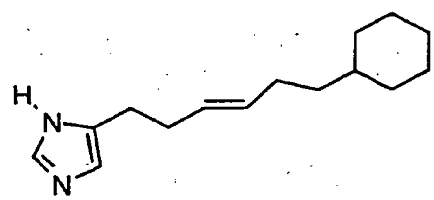
Step 2

1-[1-Triphenylmethyl-5-imidazoyl]-6-cyclohexyl-cis-3-hexene (1 gram, 2.12 mM) was dissolved in 20 cc of ethanol. 60 cc of 2N Hcl was added and the mixture heated at 90°C for 1 hour. The reaction mixture was cooled, filtered, and the filtrate neutralized with 10% NaOH solution, and then partitioned between $CHCl_3$ and water. The chloroform layer was separated, dried over Na_2SO_4, filtered, and evaporated in vacuo to obtain the crude oil. The crude product was purified using silica gel column chromatography using $MeOH/CHCl_3$, 10:90 to afford 475 mgs of 1-[1(H)-5-imidazoyl]-6-cyclohexyl-cis-3-hexene.

NMR ($CDCl_3$, 300 Mhz): d 7.52 (s, 1H), 6.76 (s, 1H), 5.38 (m, 2H), 2.65 (m, 2H), 2.36 (m, 2H), 1.98 (m, 2H), 1.64 (m, 5H), 1.22 - 1.08 (m, 6H), 0.84 (m, 2H).

Mass Spectrum (DCI/NH_3): 233 $(M+1)^+$, MW = 232.3704, $C_{15}H_{24}N_2$.
CNH Analysis: Calc.: C: 77.58, H: 10.34, N: 12.06; Found: C: 76.14, H: 10.04, N: 11.95

EXAMPLE 25



<u>Preparation of 1-[1(H)-5-imidazoyl]-6-cyclohexyl-trans-3-hexene</u>

Step 1

3-cyclohexylpropyl-p-toluene-sulfone (0.42 grams, 1.57 mMoles) was dissolved in 15 ml of dry THF and cooled to -78°C under N_2. Sodium bis(trimethylsilyl) amide (1.0 M in THF, 1.70 ml, 1.70 mMoles) was added via syringe, and the reaction stirred at -78°C for 1 hour. 3-[1-Triphenylmethyl-5-imidazoyl]-propanal (0.577 grams, 1.57 mMoles) in 25 cc of dry THF was added rapidly dropwise to the yellow green sulfone anion solution,

and the reaction stirred for an additional 30 minutes. The reaction was quenched with 200 cc of a saturated solution of ammonium chloride, and extracted with 250 cc of ethyl acetate. The ethyl acetate layer was separated, dried over $MgSO_4$, filtered, and evaporated in vacuo to give a yellow oil. The crude product was purified by silica gel column chromatography using ethyl acetate/hexanes to afford 226 mgs of a racemic mixture of 1-[1-Triphenylmethyl-5-imidazoyl]-3-hydroxy-4-phenylsulfonyl-6-cyclohexyl-hexane.

NMR ($CDCl_3$, 300 Mhz):d 7.88 (m, 2H), 7.58 (m, 1H), 7.50 (m, 2H), 7.30 (m, 9H), 7.27 (m,1H), 7.10 (m, 6H), 6.55 (two s, 1H, 1H), 4.26 (m, 1H), 4.16 (m, 1H), 3.18 (m, 1H), 2.88 (m, 1H), 2.66 (m, 1H), 2.10 (m,1H), 1.80 (m, 5H), 1.10 (m, 6H), 0.76 (m, 2H).

Step 2

1-[1-Triphenylmethyl-5-imidazoyl]-3-hydroxy-4-phenylsulfonyl-6-cyclohexyl-hexane (0.226 grams, 0.375 mMoles) was dissolved in 20 cc of dry MeOH. NaH_2PO_4 (0.30 grams) was added, and the reaction mixture placed under N_2. Na(Hg) (2% by weight, total of 7 grams) was added to the reaction mixture which was stirred for 1.5 hours. The reaction mixture was filtered through a pad of celite, washing the celite with MeOH (20 cc) and eth¥l acetate (100cc). The filtrate was evaporated in vacuo, and the residue partitioned between $CHCl_3$ and water (50/50 cc). The $CHCl_3$ layer was separated, dried over $MgSO_4$, filtered, and evaporated in vacuo. The pale yellow oil was purified by thin layer chromatography using ethyl acetate/hexanes 3:7 to afford 57 mgs of 1-[1-Triphenylmethyl-5-imidazoyl]-6-cyclohexyl-trans-3-hexene and 30 mgs of of 1-[1-Triphenylmethyl-5-imidazoyl]-6-cyclohexyl-cis-3-hexene.

NMR ($CDCl_3$, 300 Mhz): trans isomer d 7.30 (m, 9H), 7.12 (m, 7H), 6.48 (s, 1H), 5.36 (m,2H), 2.57 (m, 2H), 2.26 (m, 2H), 1.92 (m, 2H), 1.64 (m,5H), 1.16 (m, 6H), 0.82 (m, 2H).

NMR ($CDCl_3$, 300 Mhz): cis isomer d 7.30 (m, 9H), 7.12 (m, 7H), 6.49 (s, 1H), 5.32 (m,2H), 2.56 (m, 2H), 2.32 (m, 2H), 1.95 (m, 2H), 1.64 (m,5H), 1.16 (m, 6H), 0.82 (m, 2H).

Mass Spectrum: (DCI/NH_3): trans isomer and cis isomer 475 $(M+1)^+$, MW= 474.6914, $C_{34}H_{38}N_2$

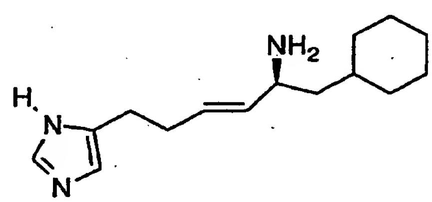
Step 3

1-[1-Triphenylmethyl-5-imidazoyl]-6-cyclohexyl-trans-3-hexene (0.057g,0.12 mMoles) was dissolved in 2 cc of ethanol. 15 cc of 2N Hcl was added and the reaction mixture heated at 90°C for 1 hour. The reaction mixture was cooled, filtered, and the organic volatiles evaporated in vacuo. The residue was partitioned between $CHCl_3$ and 10% NaOH solution. The $CHCl_3$ layer was separated, dried over $MgSO_4$, filtered, and evaporated in vacuo to give a crude yellow oil. The crude product was purified using silica gel column chromatography using $CHCl_3$/MeOH, 90:10 to give 19 mgs of a yellow oil, 1-[1-(H)-5-imidazoyl]-6-cyclohexyl-trans-3-hexene.

NMR ($CDCl_3$, 300 Mhz): d 7.56 (s, 1H), 6.76 (s, 1H), 5.43 (m, 2H), 2.64 (m, 2H), 2.30 (m,2H), 1.96 (m, 2H), 1.65 (m,5H), 1.18 (m, 6H), 0.83 (m, 2H).

Mass Spectrum (DCI/NH_3): 233 $(M+1)^+$, MW = 232.3704, $C_{15}H_{24}N_2$.

EXAMPLE 26



Preparation of 1-[1(H)-5-imidazoyl]-5-amino-6-cyclohexyl-3-hexene

Step1

3-cyclohexyl-1-N-BOC-amino-propyl-phenyl sulfone (3.5g, 9.17 mMoles) was dissolved in 80 ml of dry THF and cooled to -78°C under N_2. n-BuLi (2.5M in hexanes, 8.07 ml, 20.17 mMoles) was added dropwise via syringe, and the reaction mixture stirred for 1 hour. 3-[1-Triphenylmethyl-5-imidazoyl]-propanal (3.35g, 9.17 mmoles) was

dissolved in 80 cc of dry THF, and added to the THF solution of sulfone slowly via syringe. The reaction mixture was stirred for 1 hour after the addition was complete. The reaction was quenched by the addition of 300 cc of a saturated solution of ammonium chloride and extracted with ethyl acetate (2x100 ml). The ethyl acetate layer was separated, dried over $MgSO_4$, filtered, and evaporated in vacuo to afford a viscous yellow oil. The crude product was purified by silica gel column chromatography using ethyl acetate/hexanes (4:6), to give 3.7 grams of a white solid, the racemic mixture of 1-[1-Triphenymethyl-5-imidazoyl]-3-hydroxy-4-phenylsulfonyl-5-N-BOC-amino-6-cyclohexyl hexane.

NMR ($CDCl_3$, 300 Mhz): d 7.90 (m,2H), 7.52 (m, 3H), 7.31 (m, 9H), 7.10 (m, 7H), 6.51 (m, 1H), 5.8 (d, 1H), 4.35 (m, 2H), 3.2 (m, 1H), 2.65 (m, 2H), 2.2 - 1.0 (m, 14H), 0.82 (m, 2H).

Step 2

1-[1-Triphenymethyl-5-imidazoyl]-3-hydroxy-4-phenylsulfonyl-5-N-BOC-amino-6-cyclohexyl hexane (3.7 grams, 4.95 mMoles) was dissolved in dry methanol. Sodium hydrogen phosphate monobasic (4.92 grams, 34.6 mMoles) was added, and the reaction mixture cooled to 0°C under N_2. 2% Na(Hg) (2X 12grams) was added and the reaction stirred for 1.5 hours. After that time, a second portion of Na(Hg) (24 grams) was added, and the reaction mixture stirred for an additional hour, warming to r.t. The reaction mixture was filtered through a pad of celite, washing the pad with ethyl acetate (300 cc). The filtrate was evaporated in vacuo, and the residue remaining partitioned between $CHCl_3$ and water. The $CHCl_3$ layer was separated, dried over $MgSO_4$, filtered, and concentrated to give a yellow oil. The crude product was purified by silica gel column chromatography using ethyl acetate/hexanes (3:7) to give 1.5 grams of an oil, 1-[1-Triphenymethyl-5-imidazoyl -5-N-BOC-amino-6-cyclohexyl-3- hexene.

NMR ($CDCl_3$, 300 Mhz): d 7.31 (m, 9H), 7.12 (m, 7H), 6.50 (s, 1H), 5.56 (m, 1H), 5.30 (m, 1H), 2.58 (m, 2H), 2.32 (m, 2H), 1.78 - 1.52 (m, 12H), 1.4 (m, 6H), 1.18 (m, 4H), 0.86 (m, 2H).

Step 3

1-[1-Triphenymethyl-5-imidazoyl -5-N-BOC-amino-6-cyclohexyl-3- hexene (1.5 grams, 2.54 mMoles) was dissolved in 15 cc of ethanol. 50 cc of 2N Hcl was added and

the reaction mixture heated at 90°C for 1 hour. The reaction was cooled, filtered, and the filtrate neutralized to pH =7-8 with 10% NaOH solution, and then extracted with $CHCl_3$. The $CHCl_3$ layer was separated, dried over $MgSO_4$, filtered, and evaporated in vacuo to give a crude yellow oil. The crude product was purified by silica gel column chromatography using $CHCl_3/MeOH/NH_4OH$ (90:10:1) to afford 512 mgs of 1-[1(H)-5-imidazoyl]-5-amino-6-cyclohexyl-3-hexene.

NMR ($CDCl_3$, 300 Mhz): d 7.52 (s, 1H), 6.75 (s, 1H), 5.54 (m, 1H), 5.36 (m, 1H), 3.12 (m, 1H), 2.68 (m, 2H), 2.34 (m, 2H), 1.64 (m, 4H), 1.32 - 1.06 (m, 6H), 0.87 (m, 2H).

Mass Spectrum (DCI/NH_3): 248 $(M+1)^+$, MW = 247.3852, $C_{15}H_{25}N_3$.

The compounds of this invention are antagonists of the histamine H_3 receptor. The binding affinity of the compounds of the invention to the H_3 receptor may be demonstrated by the procedure described below:

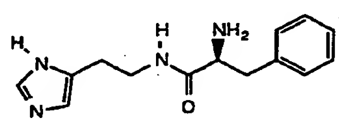
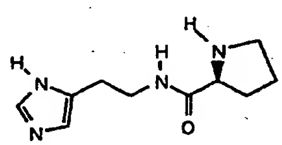
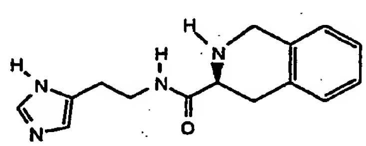
In Vitro Histamine H_3 Receptor Binding Analysis.

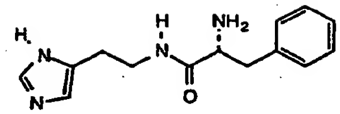
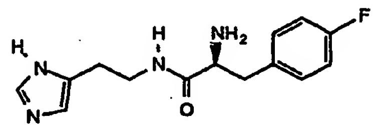
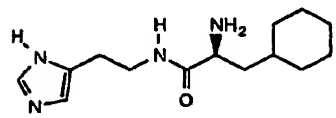
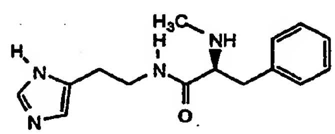
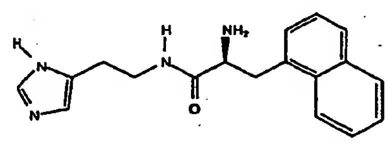
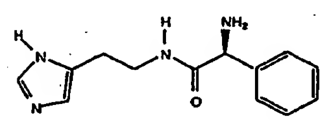
Histamine H_3 receptor affinity was determined in rat cortical membranes using the H3 selective agonist ligand, [^{3}H]-Nα-methylhistamine (78.9 Ci/mmole, DuPont NEN Research Products, Boston, MA) according to the method of West et al. (1990) with modifications. Briefly, animals were sacrificed by decapitation and the cerebral cortex was rapidly removed. Rat cortices were mechanically homogenized with an Omni 1000 motor driven homogenizer in 10 volumes (wt/vol) of Krebs-Ringers Hepes buffer (pH 7.4) containing the following protease inhibitors; EDTA (10 mM), PMSF (0.1mM), chymostatin (0.2 mg/50mL) and leupeptin (0.2 mg/50mL). The homogenate was centrifuged in a Sorvall at ~40,000 x g for 30 min. The pellet was resuspended by mechanical homogenization in 25 mL water and lysed on ice for 30 min. The homogenate was recentrifuged and the membrane lysis was repeated. The membranes were recentrifuged and the final pellet was resuspended in 14 volumes of water to give approximately 200 mg protein/100 ml final concentration. The suspension was stored at -80°C prior to use. Protein concentrations were determined by Coomassie Plus Protein Assay (Pierce, Rockford, IL).

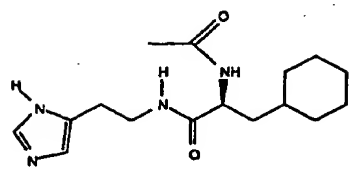
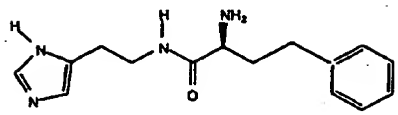
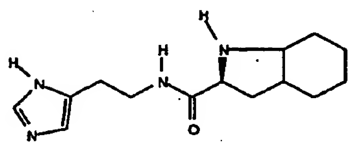
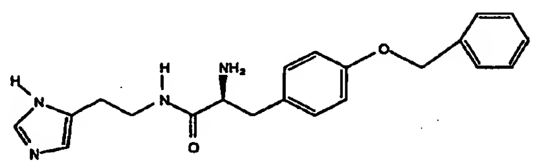
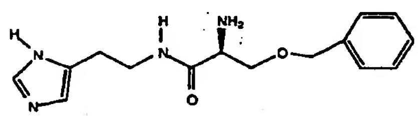
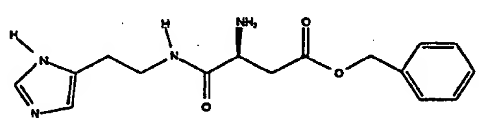
The binding assay was carried out in polypropylene tubes in a total volume of 0.4 ml of 50 mM Na^+ Phosphate buffer (pH 7.4), containing 150-200 mg of tissue protein, 0.8-1.2 nM [^{3}H]-Nα-methylhistamine and 0.3 to 10,000 nM GT-2016. Nonspecific binding (NSB) was accounted for by the inclusion of thioperamide (10 mM). The samples were incubated for 40 minutes at 25°C. Samples were filtered through glass fiber strips, pre-washed with 0.3% polyethyleneimine, using a Brandell cell harvester. The filters were rapidly washed three times with 4 ml of 25 mm Tris buffer containing 145 mM NaCl (pH 7.4, 4oC). Filters were transferred to polyethylene minivials and counted in 3.5 ml of scintillation fluid (Ecolume, ICN Biomedicals, Inc.). Using this procedure, the non-specific binding was less than 10% of the total binding and the binding to the glass fiber filters was negligible. Saturation and competition experiments were analyzed with the ReceptorFit saturation and competition curve fitting programs (Lundon Software, Inc., Cleveland, OH). K_i's were determined using the equation $K_i = IC_{50}/(1 + ([\text{Ligand}]/[K_d]))$. The results are given in Table 1.

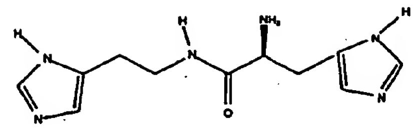
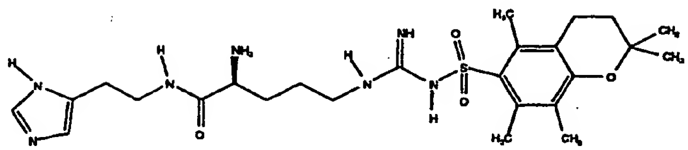
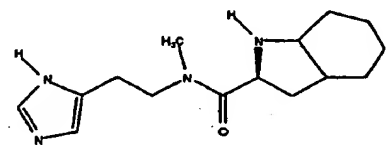
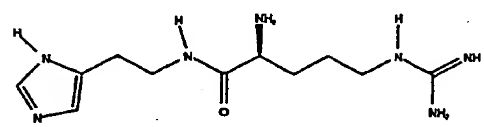
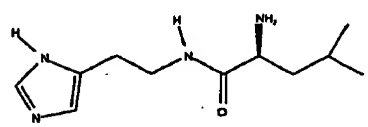
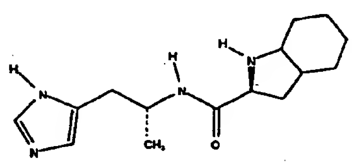
TABLE 1

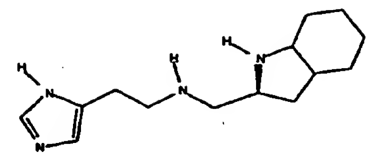
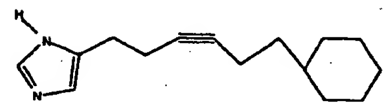
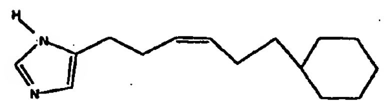
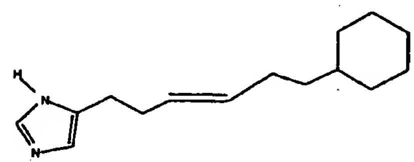
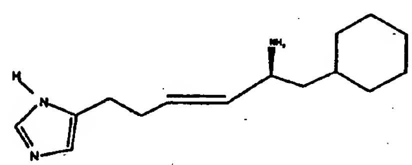
Histamine H3 Receptor Binding Affinities

Example #	Structure	H3 Receptor (K_i nM)
1		104 ±14
2		202 ±2
3		82.7 ±7.7

4		>10,000
5		84.5 ±12.8
6		30.8 ±2.1
7		1650 ±310
8		299 ±82
9		630 ±51

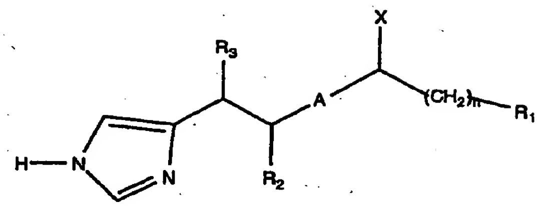
10		5485 ±255
11		10.9 ±1.7
12		11.1 ±0.4
13		199 ±24
14		122 ±11
15		81.6 ±13.6

16		3256 ±457
17		14 ±3
18		45 ±1.1
19		63 ±1
20		122 ±37
21		231 ±15

22		66 ± 4
23		2.9 ± 0.2
24		4.2 ± 0.6
25		16 ± 2
26		1.0 ± 0.1

WHAT IS CLAIMED IS:

1. A compound of the formula:



(1.0)

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

where A is -NHCO-, $-N(CH_3)-CO-$, $-NHCH_2-$, $-N(CH_3)-CH_2-$, -CH=CH-, $-COCH_2-$, $-CH_2CH_2-$, $-CH(OH)CH_2-$, or $—C{\equiv}C—$;

X is H, CH_3, NH_2, $NH(CH_3)$, $N(CH_3)_2$, OH, OCH_3, or SH;

R_2 is hydrogen or a methyl or ethyl group;

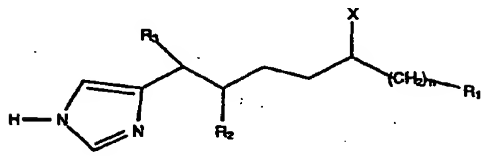
R_3 is hydrogen or a methyl or ethyl group;

n is 0, 1, 2, 3, 4, 5, or 6; and

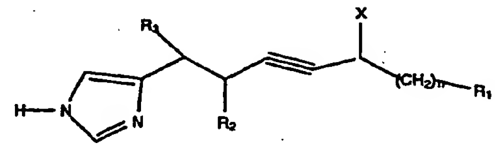
R_1 is selected from the group consisting of (a) C_3 to C_8 cycloalkyl; (b) phenyl or substituted phenyl; (d) heterocyclic; (e) decahydronaphthalene and (f) octahydroindene; or

R_1 and X may be taken together to denote a 5,6 or 6,6 saturated bicyclic ring structure when X is NH, O, or S.

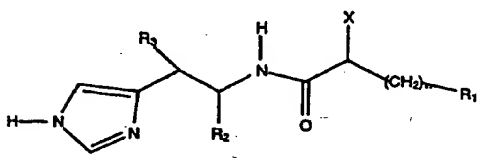
2. A compound or a pharmaceutically acceptable salt or hydrate thereof, as in claim 1 selected from the group consisting of:



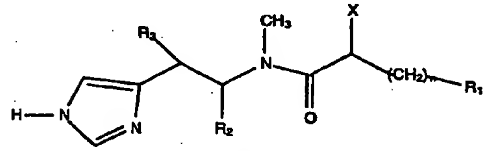
(2.0)



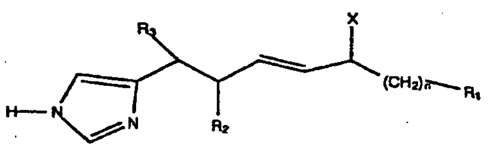
(3.0)



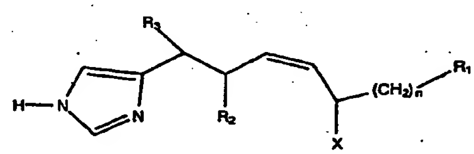
(4.0)



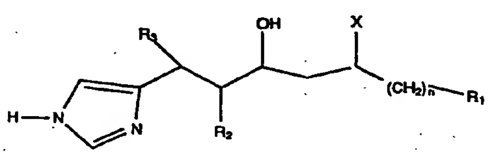
(5.0)



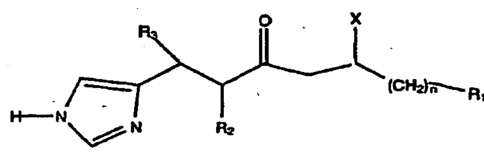
(6.0)



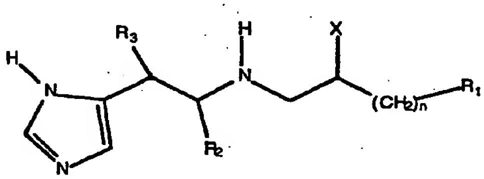
(7.0)



(8.0)

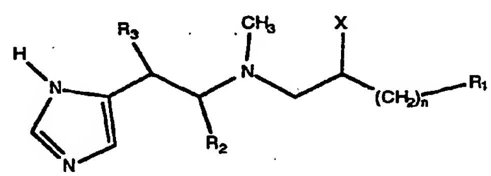


(9.0)



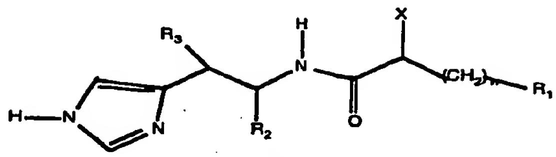
(10.0)

and



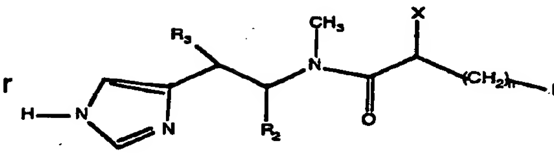
(11.0)

3. A compound as in claim 2 having the formula:



(4.0)

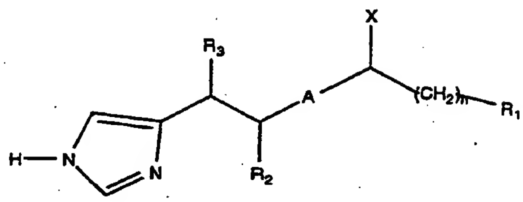
or



(5.0)

where R_1, R_2 R_3, n and X are as defined in claim 1.

4. A compound of the formula:



(1.0)

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

A is $-NHCH_2-$, $-N(CH_3)-CH_2-$, -CH=CH-,

$-COCH_2-$, $-CH_2CH_2-$, $-CH(OH)CH_2-$, or $-C\equiv C-$;

X is H, CH_3, NH_2, $NH(CH_3)$, $N(CH_3)_2$, OH, OCH_3, or SH;

R_2 is hydrogen or a methyl or ethyl group;

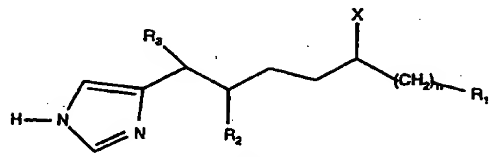
R_3 is hydrogen or a methyl or ethyl group;

n is 0, 1, 2, 3, 4, 5, or 6; and

R_1 is selected from the group consisting of (a) C_3 to C_8 cycloalkyl; (b) phenyl or substituted phenyl; (d) heterocyclic; (e) decahydronaphthalene and (f) octahydroindene; or

R_1 and X may be taken together to denote a 5,6 or 6,6 saturated bicyclic ring structure when X is NH, O, or S.

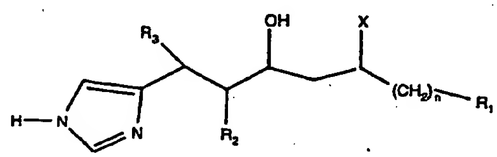
5. A compound as in claim 4 having the formula:



(2.0)

where R_1, R_2 R_3, n and X are as defined in claim 4.

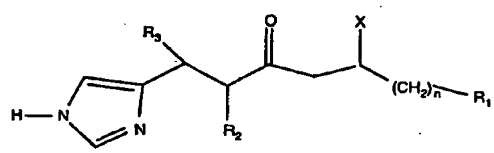
6. A compound as in claim 4 having the formula:



(8.0)

where R_1, R_2 R_3, n and X are as defined in claim 4.

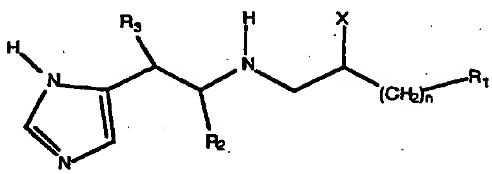
7. A compound as in claim 4 having the formula:



(9.0)

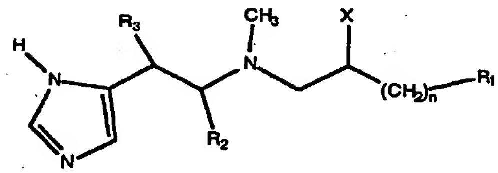
where R_1, R_2 R_3, n and X are as defined in claim 4.

8. A compound as in claim 4 having the formula:



(10.0)

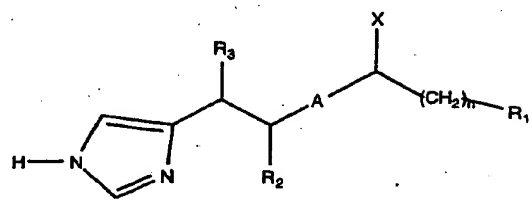
or



(11.0)

where R_1, R_2 R_3, n and X are as defined in claim 4.

9. A compound of the formula:



(1.0)

or a pharmaceutically acceptable salt or hydrate thereof,

where A is -CH=CH or $-C \equiv C-$;

X is H, CH_3 or NH_2;

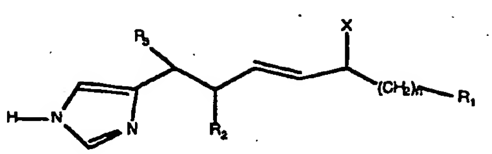
R_2 and R_3 are H;

n is 1, 2, or 3;

R_1 is selected from the group consisting of (a) C_3 to C_8 cycloalkyl; (b) phenyl or substituted phenyl; (d) heterocyclic; (e) decahydronaphthalene and (f) octahydroindene; or

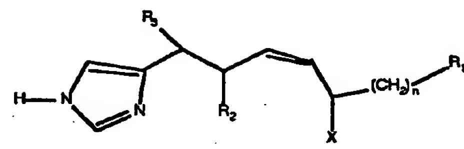
R_1 and X may be taken together to denote a 5,6 or 6,6 saturated bicyclic ring structure, when X is NH, O, or S.

10. A compound as claimed in claim 9 having the formula:



(6.0)

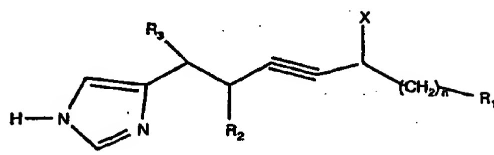
or



(7.0)

wherin R_1, R_2 R_3, n and X are as defined in claim 9.

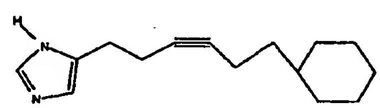
11. A compound as in claim 9 having the formula:



(3.0)

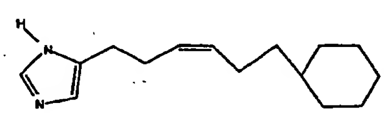
wherin R_1, R_2 R_3, n and X are as defined in claim 9.

12. A compound as in claim 9, having the structure:



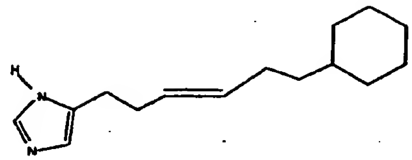
or a pharmaceutically acceptable salt therof.

13. A compound as in claim 9, having the structure:



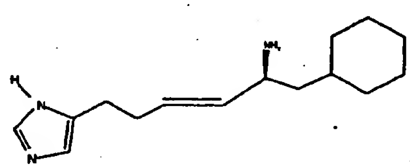
or a pharmaceutically acceptable salt therof.

14. A compound as in claim 9, having th structure:



or a pharmaceutically acceptable salt therof.

15. A compound as in of claim 9, having the structure:



or a pharmaceutically acceptable salt therof.

16. A pharmaceutical composition comprising at least one compound of claim 1 and a pharmaceutically acceptable carrier.

17. A method of preparing a pharmaceutical composition comprising admixing a compound of claim 1 with a pharmaceutically acceptable carrier.

18. A method of treating allergy, inflammation, cardiovascular disease (i.e. hyper or hypotension), gastrointestinal disorders (acid secretion, motility) and CNS disorders involving attention or cognitive disorders, (i.e., Alzheimer's, Attention Deficit Disorder, age-related memory dysfunction, stroke, etc.), CNS psychiatric and motor disorders (i.e., depression, schizophrenia, obsessive-compulsive disorders, tourette's syndrome, etc.) and sleep disorders (i.e. narcolepsy, sleep apnea, insomnia, disturbed biological and circadian rhythms, hyper and hyposomnolence, and related sleep disorders), epilepsy, hypothalamic dysfunction (i.e., eating disorders such as obesity, anorexia/bulimia, thermoregulation, hormone release) comprising administering an effective amount of a compound of claim 1 to a patient in need of such treatment.

19. A method of antagonizing histamine H_3 receptors comprising administering to said H_3 receptors an effective amount of at least one compound of claim 1.

20. A method of preparing a pharmaceutical composition comprising admixing at least one compound of Claim 1 with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/07873

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 31/415; C07D 233/60
US CL :514/400; 548/338.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/400; 548/338.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS Online Structure Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,010,095 A (G.J. Sterk, et al.) 23 April 1991, see entire document.	1-17 and 20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 AUGUST 1996	30 SEP 1996

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	PATRICIA MORRIS jd
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/07873

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-17 and 20

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/07873

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

I.Claims 1-17 and 20, drawn to compounds, compositions and process of preparing, classified in Class 548, subclass 335.1.
Claim 18, drawn to a method of treating allergy, classified in Class 514, various subclasses.

II.Claim 18, drawn to a method of treating inflammation, classified in Class 514, various subclasses

III.Claim 18, drawn to a method of treating cardiovascular disease, classified in Class 514, various subclasses.

IV.Claim 18, drawn to gastrointestinal disorders, classified in Class 514, various subclasses.

V.Claim 18, drawn to a method of treating CNS disorders involving attention or cognitive disorders, classified in Class 514, various subclasses.

VI.Claim 18, drawn to a method of treating CNS psychiatric disorders and motor disorders, classified in Class 514, various subclasses.

VII.Claim 18, drawn to a method of treating sleep disorders, classified in Class 514, various subclasses.

VIII.Claim 18, drawn to a method of treating epilepsy, classified in Class 514, various subclasses.IX.Claim 18, drawn to a methodof treating hypothalamic dysfunction, classified in Class 514, various subclasses.

X.Claim 19, drawn to a method of antagonizing histamine H3 receptors, classified in Class 514, various subclasses.
The inventions listed as Groups I-X do not meet the requirements for Unity as Invention because Groups II-X are drawn to multiple methods of use that are distinct treatments of physiologic disorders and are separately classified. In accordance with PCT Rule 13.2, claims are permitted to one product, one process of manufacturing and one use as the main invention. 37 CFR 1.475(d).